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TREATMENT OF EXPERIMENTAL RENAL HYPERTENSION WITH PARTIALLY PURIFIED RENIN

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IN 1941, two of us¹ reported that daily intramuscular injections of partially purified hog renin for four months produced striking reductions in the blood pressures of dogs with experimental renal (Goldblatt) hypertension, whereas heat-inactivated hog renin and active dog renin were without antipressor effect. Moreover, daily intramuscular injections of hog renin solution into two dogs for three months before and three months after constriction of the renal arteries prevented the development of hypertension. The serums of the dogs treated with hog renin, but not the serums of the dogs that received injections of inactivated hog renin or dog renin, neutralized the acute pressor effect of renin (antirenin). In this report, we emphasized the fact that additional experiments were necessary in order to establish definitely the prophylactic and therapeutic value of renin solutions in experimental renal hypertension in the dog, as well as to clarify the mechanisms involved.

Experiments have now been completed in which the prophylactic effects of hog renin, inactivated hog renin, dog renin, rabbit renin, inactive human renin, and an extract of liver have been studied. Moreover, we have investigated the therapeutic effects of a second course of hog renin on hypertensive dogs that had previously been successfully treated with hog renin, and also the therapeutic effects of hog renin on hypertensive dogs which did not show an antipressor response to a previous course of inactivated hog renin or active dog renin, respectively.¹ These prophylactic and therapeutic experiments constitute the basis for the present report.

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METHODS

The methods used were, in general, similar to those previously employed.¹ Mean blood pressure readings were obtained by puncture of a femoral artery (method of Dameshek and Loman²) two or three times a week. Studies on the blood urea nitrogen, urinalyses, and determinations of the body weight were made at monthly or bimonthly intervals, and more frequently when indicated. With the exception of one experiment with highly purified hog renin, the method used for the preparation of the renin solutions was essentially that described by Grossman,³ except that acetone was employed as a dehydrating agent, and much of the associated protein was removed by isoelectric precipitation. These renin solutions were therefore *only partially purified, and obviously contained substances other than renin*. The highly purified renin was prepared from the partially purified renin by the method of one of us,⁴ using a series of precipitations which removed 84 per cent of the nonrenin substances without appreciably affecting the amount of pressor activity. With two exceptions, the renin solutions were equivalent to 1 Gm. of fresh kidney cortex per c.c. of solution. In the case of highly purified hog renin, however, the solution was equivalent to 5 Gm. of fresh kidney cortex per c.c. of solution, and when the dosage of partially purified hog renin was doubled in certain therapeutic experiments, the solution was equivalent to 2 Gm. of fresh kidney cortex per c.c. of solution. All of the renin solutions contained 0.5 per cent phenol.

Treatment consisted of daily intramuscular injections of the renin solutions. Unless otherwise stated, the dosage was 1 Gm. of fresh kidney cortex equivalent per kg. of body weight. In the prophylactic experiments, the dogs were treated with renin solutions for a period of approximately six months. In the middle of this period the right and left renal arteries were constricted, three weeks apart, by the Goldblatt technique.⁵ Four dogs were treated with hog renin, four with hog renin inactivated by heating at 70° C. for one-half hour, four with dog renin, two with rabbit renin, two with inactive human renin (renal extract prepared like renin, but pressor inactive), and three with liver extract prepared after the manner of renin. In the therapeutic experiments, unless otherwise stated, a course of renin therapy occupied a period of four months. All of the seven hypertensive dogs in this group had previously been subjected to one course of renin injections, and the results reported.¹ For four of the dogs this first course consisted of hog renin; for two, inactivated hog renin; and for one, dog renin. In the experiments reported here, all of these dogs were given hog renin injections.

Blood serums were examined for antirenin before treatment, and subsequently during treatment, at semimonthly intervals, and, after treatment, at monthly and bimonthly intervals. The technique, previously described,⁶ consisted essentially in mixing two volumes of serum with one volume of renin solution, allowing the mixture to stand at least overnight at 4° C., and assaying the acute pressor effect produced by giving the mixture intravenously to the etherized, nephrectomized dog. The dose of renin solution was 0.25 Gm. of kidney cortex equivalent per kg. of assay animal. In all instances the serum tested for antirenin was suitably controlled with serum from untreated, normal dogs, and frequently with serum from untreated hypertensive dogs. Antirenin titers were regularly ascertained for dog renin, less frequently for hog renin, and exceptionally (two dogs receiving rabbit renin) for rabbit renin.

RESULTS

I. PROPHYLACTIC EXPERIMENTS.—

Hog Renin.—During three months of hog renin injections prior to constriction of the renal arteries, the blood pressures of the four dogs in this group showed no significant change from the normal levels observed during a preceding control period of two to three months. Sub-

sequent to constriction of the renal arteries, two of the dogs showed no important change in blood pressure during the remaining three months of treatment with hog renin or during observation periods of eleven and thirteen months, respectively, after renin therapy. The results with one of these two dogs are shown in Fig. 1. The third dog showed a very moderate, but significant, rise in blood pressure after constriction of the renal arteries, with a gradual increase in the hypertension during the seven months of observation subsequent to treatment. After constriction of the renal arteries, the fourth dog developed pronounced hypertension which persisted without essential alteration during the seven months of observation subsequent to the injections of hog renin (Fig. 2).

Inactivated Hog Renin.—During the three months of inactivated hog renin injections prior to constriction of the renal arteries, the blood pressures of the four dogs remained at the normal levels that obtained during the initial control period of two and one-half months. One dog continued to have a normal blood pressure despite the renal artery constrictions. Normal pressure persisted in this animal during three months of continued inactivated hog renin injections and seven months of subsequent observation. After constriction of the renal arteries, hypertension developed in the three remaining dogs. No significant changes occurred in the hypertension of these three dogs during the ensuing three months of continued inactivated hog renin injections or during the seven months of observation after the completion of the injections.

Dog Renin.—There were no significant deviations from the initial control levels in the blood pressures of this group of four dogs during the three months of injections of dog renin prior to bilateral renal artery constriction. Two of the dogs continued to have a normal blood pressure after renal artery constriction. The blood pressure of one of these continued to be normal during the three months of continued dog renin treatment and during the seven months of observation subsequent to dog renin injections. The other animal's pressure remained within normal limits during the period of dog renin injections after the arterial constrictions, but showed a gradual, though significant, rise in blood pressure during the seven months succeeding dog renin injections. The two remaining dogs developed hypertension after the arterial constrictions. The hypertension of these two animals continued essentially unchanged during three months of continued dog renin injections and seven months of observation subsequent to the termination of the injections.

Rabbit Renin.—The normal pressure of the two dogs in this group was not altered during the first three months of rabbit renin injections. After constriction of the renal arteries the pressures continued to be normal. Shortly after constriction of the second renal artery, one of the two dogs died of pneumonia. The other animal retained a persistently normal pressure, not only during the three additional months of rabbit

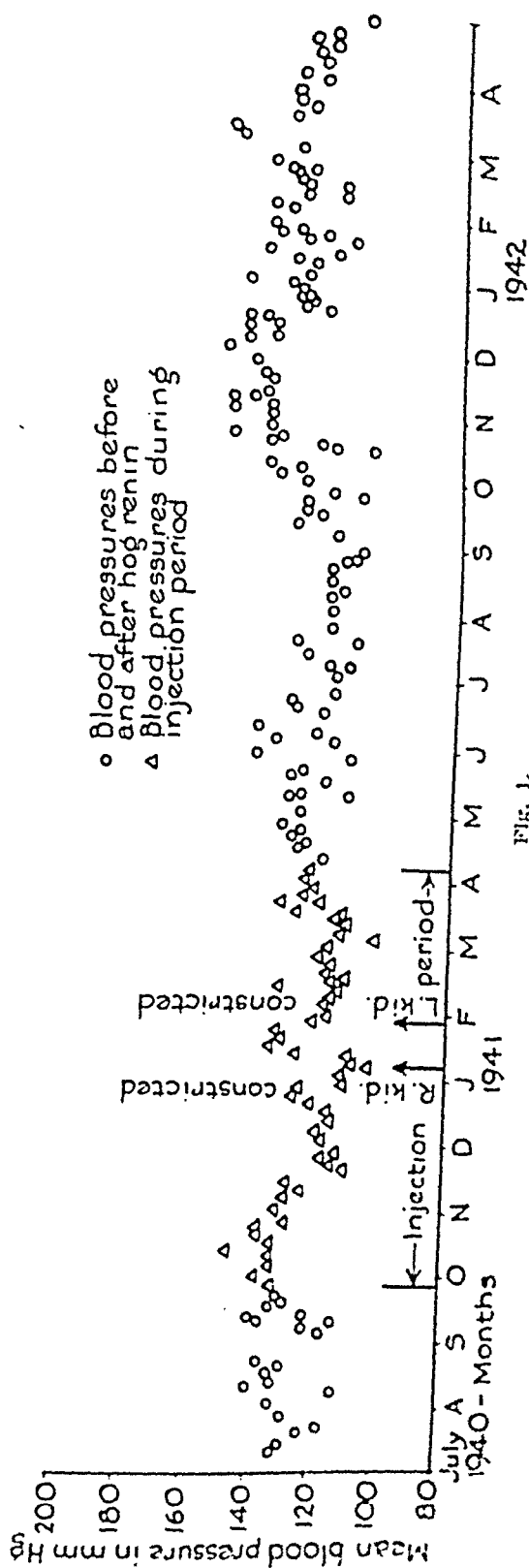


FIG. 1.

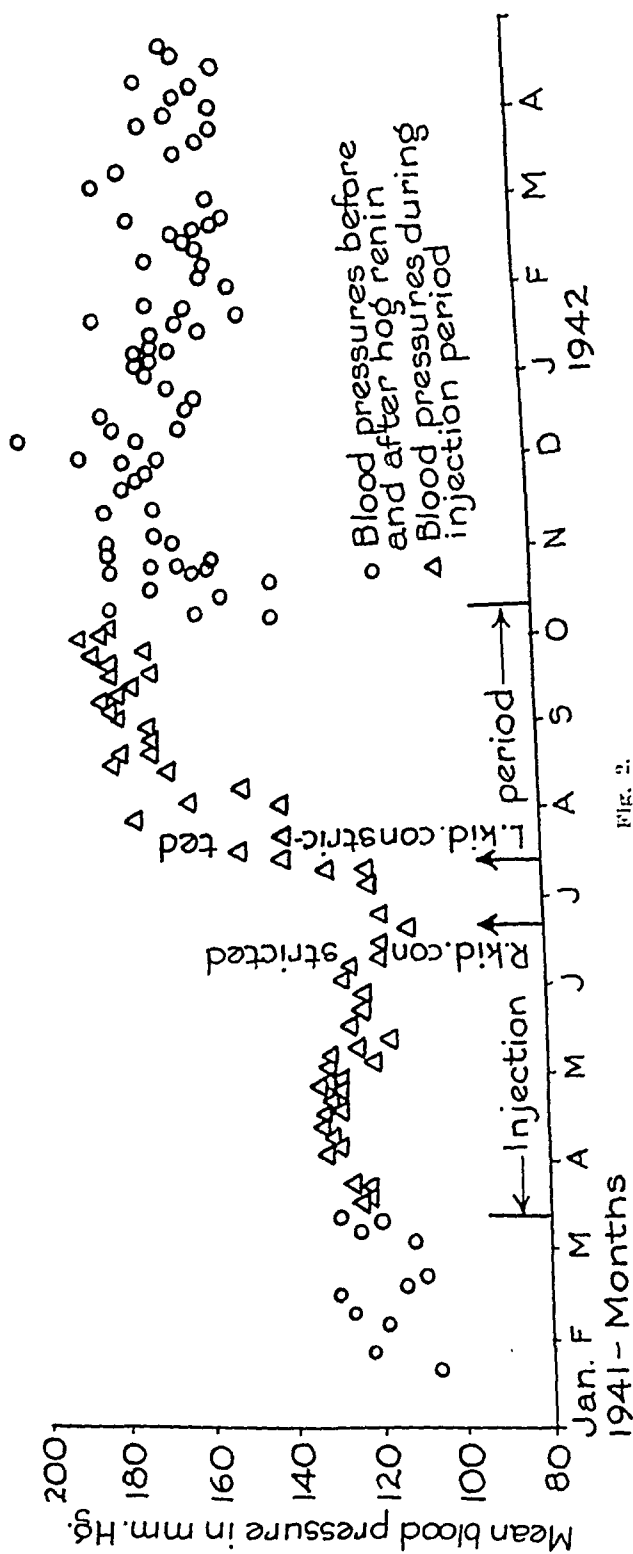


FIG. 2.

renin injections, but also during the seven months subsequent to rabbit renin treatment.

Inactive Human Renin.—The normal pressure of two dogs during the initial control period was unchanged by three months of inactive human renin injections prior to constriction of the renal arteries. Renal artery constriction produced hypertension in both animals, and one of the dogs died of malignant hypertension two weeks subsequent to the arterial constriction. The hypertension of the other animal persisted during the remaining three months of inactive human renin injections and during the three months which have elapsed since treatment was stopped.

Liver Extract.—The normal pressure of the three dogs in this group did not show any significant changes during the preconstriction injection period. After constriction of the renal arteries, all three of the dogs developed hypertension. Two weeks subsequent to the second operation, one of the dogs died of malignant hypertension. The other two dogs have shown no significant change in their hypertension during the postconstriction injection period.

Untreated Controls.—After two to four months of control blood pressure readings, sixteen dogs were subjected to bilateral renal artery constriction. After the constrictions, all of the dogs developed hypertension. These control dogs showed persistent hypertension during the five to seven months of observation subsequent to constriction.

Antirenin became demonstrable in the serums of the four dogs that received hog renin and the two dogs which were given rabbit renin during the second month of treatment, and disappeared during the second month, after treatment was discontinued. Antirenin assays were repeatedly negative in the dogs which received inactivated hog renin, dog renin, inactive human renin, and liver extract, as well as in the untreated controls.

No toxic effects from the injections were detected in any of the animals. Their appetites remained excellent, their weights constant, and their blood urea nitrogen and urine normal, throughout.

II. THERAPEUTIC EXPERIMENTS.—

Hog Renin (Preceded by Hog Renin).—The first hypertensive dog showed a decrease in blood pressure to normal or even subnormal levels during the first course of hog renin treatment. After the completion of therapy there was a slow return over a period of seven months to the pretreatment hypertensive range, where the pressure remained for the next five months that concluded the period of observation reported in our previous communication.¹ During the succeeding five months, however, the blood pressure of this animal fluctuated from normal to definitely hypertensive levels. Then the second course of hog renin injections was begun. These fluctuations in blood pressure have continued without noteworthy change during the six months of treatment, despite doubling of the hog renin dosage during the last three months (Fig. 3).

The second dog showed a decrease in blood pressure to the normal level during the first course of hog renin therapy, with a gradual increase during the four months after treatment to a hypertensive level approximately 20 mm. Hg below the pretreatment hypertensive range. During the succeeding four months the dog's pressure continued unchanged; this concluded the period of observation reported in our previous communication.¹ Four months subsequently, with the hypertensive level unaltered, the dog was subjected to a second course of hog renin. Again a prompt decrease in blood pressure to low normal levels occurred. Three months after the completion of the second course the pressure was still normal, although it then began to rise (Fig. 4).

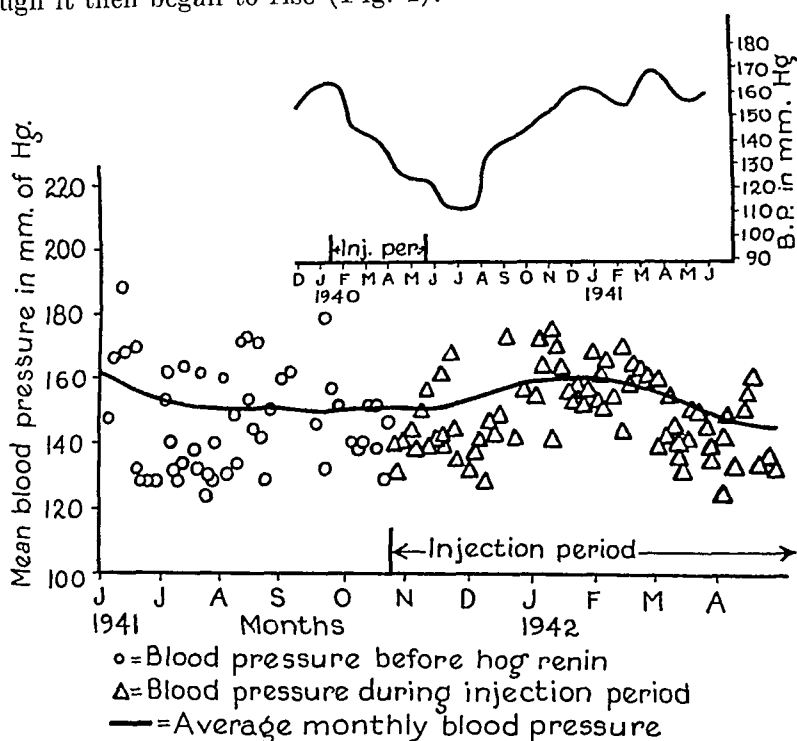


Fig. 3.

In the third dog, the first course of hog renin reduced the blood pressure to normal levels; this was followed by a gradual return to the pretreatment hypertensive level over a period of five months after therapy. For the next three months there was no significant change in this animal's hypertension.¹ Three months later, with the hypertension unaltered, the dog was started on a second course of hog renin. Since no significant change in blood pressure resulted during the four months of treatment, the hog renin dosage was doubled. Four additional months of therapy at this dosage have resulted in a decrease in blood pressure to normal levels (Fig. 5).

The fourth dog showed a significant reduction in blood pressure, although not to normal levels, as a result of the first course of hog renin. Subsequent to treatment the blood pressure returned to its pretreatment

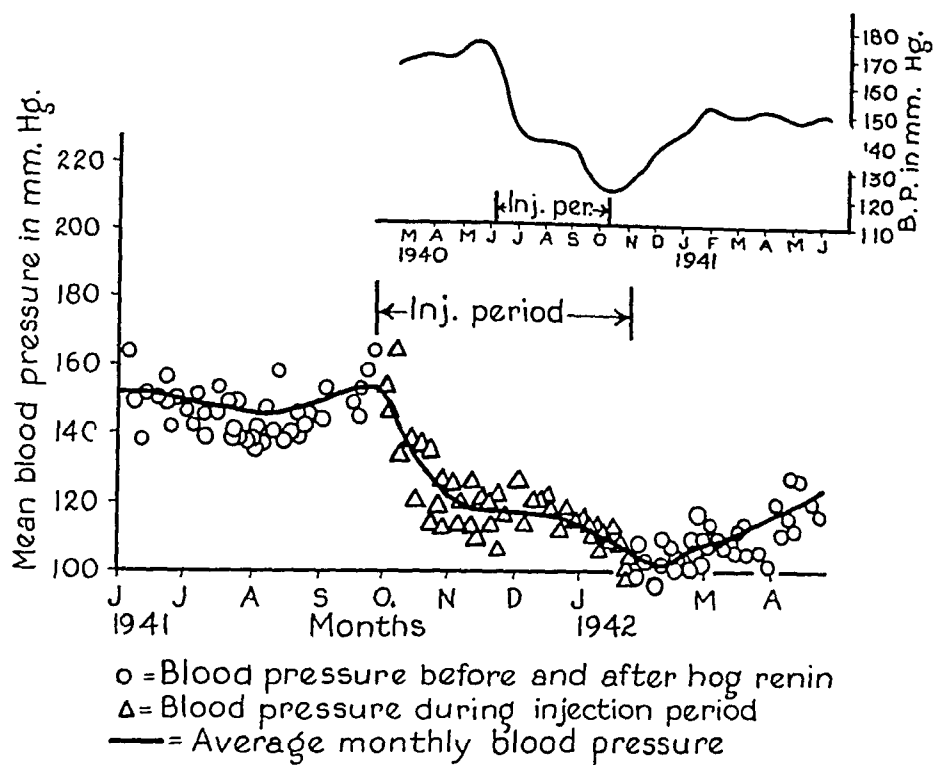


Fig. 4.

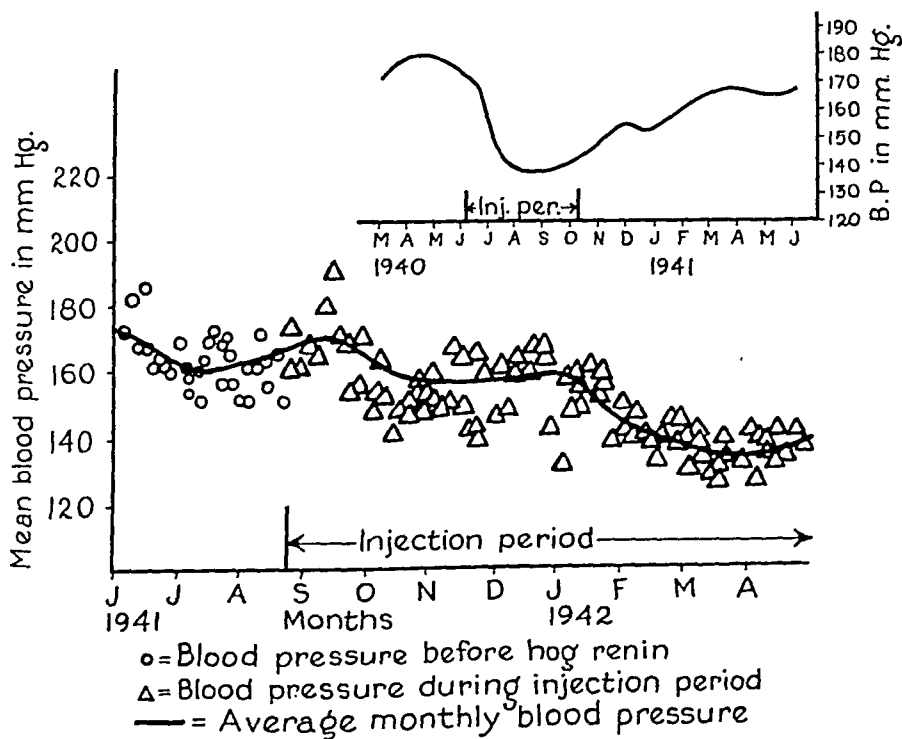


Fig. 5.

hypertensive level over a period of four months, where it remained during the next four months.¹ Two months later, the dog was given a second course of hog renin. This produced a reduction in blood pressure strikingly similar to that which resulted from the first course. Subsequent to therapy, the pressure gradually increased to the pretreatment hypertensive level over a period of five months (Fig. 6).

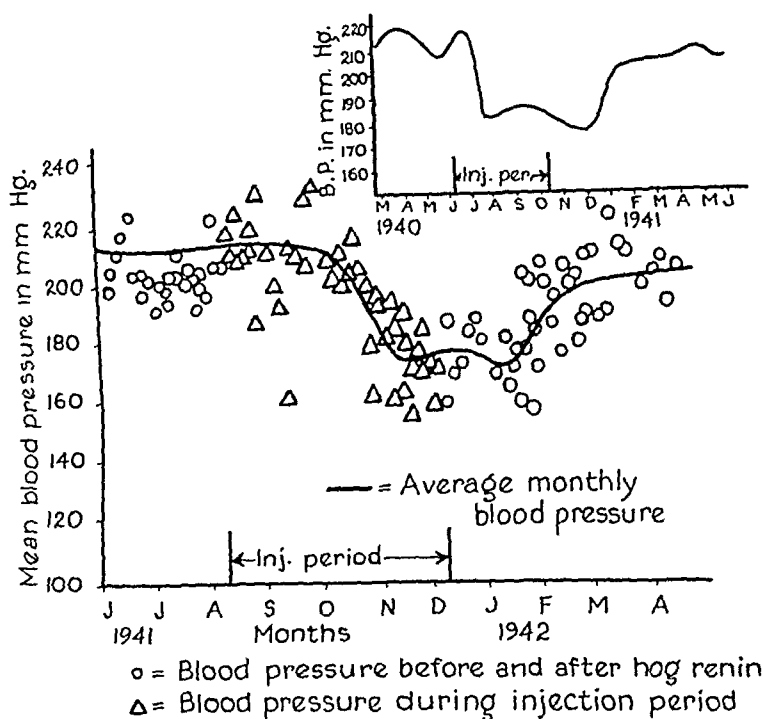


Fig. 6.

Antirenin became demonstrable in the serums of these four dogs during the second month of the first course of hog renin therapy. Antirenin disappeared from the first dog during the seventeenth month after treatment, whereas the renin neutralizing body was no longer demonstrable in the other three dogs by the seventh, fifth, and sixth months, respectively, after treatment.¹ After instituting the second course of hog renin, antirenin reappeared in the serums of the four dogs during the second week of therapy. The first and third dogs are still under treatment, and, obviously, antirenin continues to be present. Antirenin has persisted to date in the second and fourth dogs, three and five months, respectively, after the completion of treatment.

Hog Renin (Preceded by Inactivated Hog Renin).—The first hypertensive dog of this group showed no significant change in blood pressure as a consequence of a course of inactivated hog renin injections.¹ Two weeks later, an eight months' course of highly purified hog renin was instituted. Since this produced no significant effect, it was followed by a course of partially purified hog renin, which produced a slight, but probably significant, decrease in blood pressure during the fourth

month. However, when the dosage of partially purified hog renin was then doubled, a gradual reduction in blood pressure to the normal level for the animal occurred during the ensuing three months of treatment with the larger dose (Fig. 7).

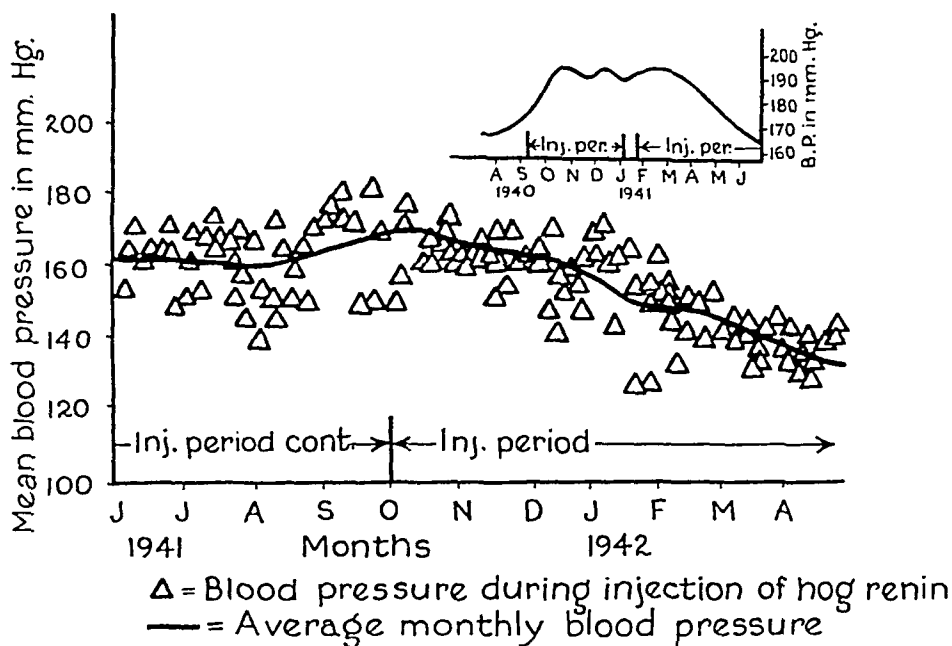


Fig. 7.

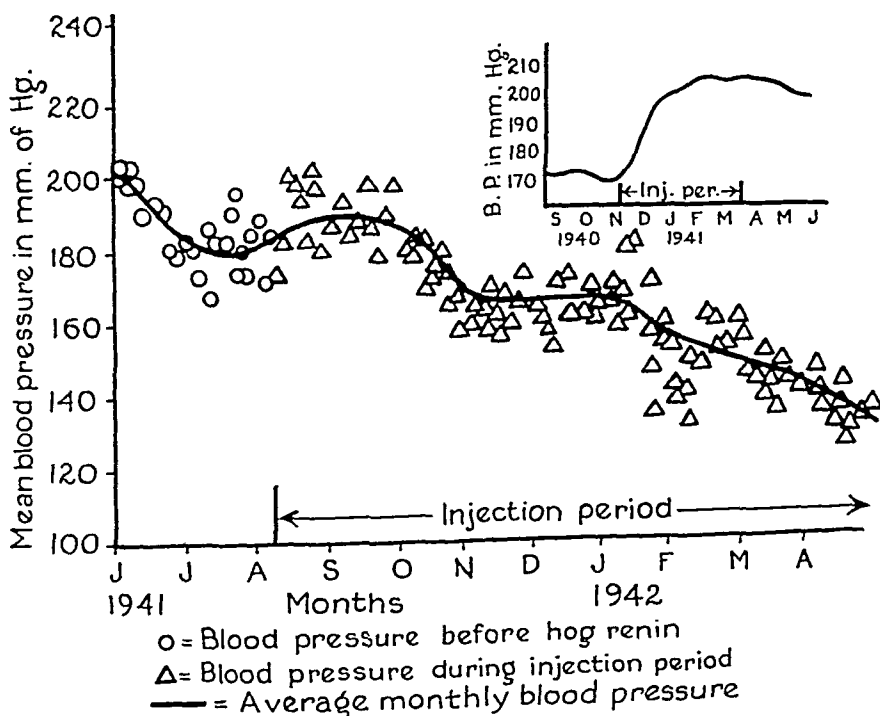


Fig. 8.

The second dog likewise showed no significant change in blood pressure during or following a course of inactivated hog renin.¹ Two weeks after the inactivated hog renin, the dog was given an eight months'

course of hog renin in one-quarter the usual dosage, without any effect on the animal's hypertension. Subsequent to this, and, for the past seven months, the dog has been used for the assay (with negative results) of the antipressor action of a different type of kidney extract, not germane to the present discussion.

No antirenin developed in the serums of these two dogs as a result of the inactivated hog renin injections.¹ During the second month of (active) hog renin, however, antirenin became demonstrable in both dogs. The renin neutralizing body has persisted to date in the first dog, which is still under therapy, but disappeared from the serum of the second animal during the third month after treatment with hog renin was discontinued.

Hog Renin (Preceded by Dog Renin).—One dog showed a significant increase of approximately 30 mm. Hg in its hypertension during an initial course of dog renin.¹ The blood pressure gradually decreased to the pretreatment hypertensive range over a period of five months after dog renin. The dog was then given a five months' course of hog renin without any significant effect on the hypertension. When the dosage of hog renin was doubled, the blood pressure of the animal gradually decreased to normal levels during four months of additional therapy with the larger dose (Fig. 8).

The course of dog renin did not result in the appearance of antirenin in the serum of this dog.¹ During the second month of hog renin injections, however, antirenin became demonstrable, and persisted during nine months of hog renin treatment.

As previously reported for the first courses of injections which these seven hypertensive dogs received,¹ the later courses of treatment with the hog renins reported in this communication were without any detectable local or general toxic effects.

COMMENT

The prophylactic experiments constitute the first successful prevention of experimental renal hypertension in the dog; a number of unsuccessful attempts have previously been reported. Thus, renal artery denervation,⁷⁻⁹ splanchnicotomy,¹⁰ anterior root section,¹¹ buffer nerve section,¹² complete sympathectomy,¹³⁻¹⁵ and destruction of the spinal cord below the fifth cervical segment¹⁶ did not prevent the development of experimental renal hypertension after constriction of the renal arteries in dogs. Page and Sweet¹⁷ found that previous hypophysectomy in dogs decreased the hypertension resulting from renal artery constriction, but did not prevent it. Thyroidectomy¹⁸ and gonadectomy¹⁹ did not interfere with the production of experimental renal hypertension. Collins and Wood²⁰ reported that adrenalectomy diminished, but did not prevent, the hypertension consequent upon renal artery constriction in dogs. Page, Patton, and Ogden²¹ found that pregnancy frequently delayed the onset of experimental renal hypertension in rats.

Our results show that, of a total of fifteen dogs treated with renal extracts, six (40 per cent) were protected against hypertension and nine were not. This is in striking contrast to the control group of sixteen untreated dogs, all of which became hypertensive. In a larger series of 75 untreated dogs which were operated upon by essentially the same technique during the past three years, we have failed to obtain some degree of hypertension in only one animal. Others²² have reported failure to obtain hypertension after constriction of the renal arteries by a somewhat different technique in 10 per cent of their dogs.

The long periods of normal pressure in five of the protected dogs after the discontinuance of treatment are striking. We intend to observe these animals for a minimum of eighteen months subsequent to treatment. If these five dogs do not become hypertensive during this observation period, we shall further constrict the renal arteries until hypertension, malignant hypertension, or fatal uremia without hypertension results. The fact that only one per cent of our untreated dogs failed to develop at least some degree of hypertension after constriction of the renal arteries renders most unlikely the possibility that the persistence of normal pressure was unrelated to the renal extracts injected. That they constitute true instances of successful prophylaxis is also attested by the fact that one dog which received dog renin was protected only during the period of treatment, and that one dog that was partially protected by hog renin showed a further increase in blood pressure after treatment.

The mechanism of these prophylactic effects is not apparent at present. Obviously, the small number of animals in each prophylactic group and the lack of consistent results within each group make a final interpretation impossible. Whether the prophylactic effects are due to *renin or to some other substance or substances in the partially purified solutions* is likewise not ascertainable at present. The evidence that the prophylactic effects are not brought about by antirenin appears conclusive. Thus, two dogs which received dog renin and one that was given inactivated hog renin were protected against experimental renal hypertension, although these animals never at any time showed antirenin in their serums. Furthermore, the two dogs treated with hog renin and the one treated with rabbit renin, which were protected against hypertension, continued to have a normal pressure for months after the disappearance of antirenin from their serums. Nevertheless, some other type of antihormone or immune response is not completely ruled out.

The results of the therapeutic experiments amply confirm the previously reported effectiveness of hog renin solution in experimental renal hypertension in the dog. Thus, the second and fourth dogs, which received two courses of hog renin, again showed a decrease in blood pressure to normal levels as a consequence of the second course of hog renin. The third dog responded to the second course of hog renin after the dosage was doubled. The first dog has thus far not responded even to

an increased hog renin dosage, although this animal obtained an excellent therapeutic result from the first course of hog renin. Of the two dogs which had previously received a course of inactivated hog renin without showing any antipressor effect, one did not respond to highly purified hog renin or to partially purified hog renin, but did respond with a decrease in blood pressure to normal when the partially purified hog renin dosage was doubled. The other dog did not respond to hog renin in reduced dosage. The dog which had previously received a course of dog renin without antipressor effect regained normal blood pressure under a course of hog renin, although only after the dosage was doubled.

The mechanism of these reductions in blood pressure which are produced in experimental renal hypertension by hog renin is not yet clear. Whether the therapeutic effects of hog renin are due to *renin or to some other principle or principles in the partially purified solution* cannot be stated at present. The recent statement by Friedman, et al.,²³ that highly purified hog renin is without antipressor effect in renal hypertensive dogs is wholly inconclusive in this connection, for the dose which they employed was only one-twentieth of our minimum in terms of renin, although the same in terms of fresh kidney cortex equivalent. Almost certainly, our therapeutic effects were not due to antirenin. Thus, in the first hypertensive dog, which received two courses of hog renin, the blood pressure returned to the pretreatment hypertensive level after the first course, in spite of the persistence of antirenin in the serum. Moreover, despite the prompt reappearance of antirenin during the second course, there has thus far been no significant reduction of this animal's blood pressure. The third dog, which received two courses of hog renin, showed no therapeutic effects from the second course of hog renin, despite the prompt reappearance of antirenin, until the dosage of hog renin was doubled. Likewise, the two dogs that were first treated with inactivated hog renin did not show therapeutic effects after eight months of highly purified hog renin or eight months of partially purified hog renin (in reduced dosage), respectively, although antirenin became demonstrable in their serums during the second month of treatment with the hog renins. Similarly, the hypertensive dog which first received a course of dog renin showed no therapeutic response from the course of hog renin until the dosage was doubled, although antirenin was produced by the initial hog renin dosage.

As stated above, we observed a notable lack of toxic effects from the injections of these kidney extracts into both normal and hypertensive dogs, although the most sensitive tests for renal, hepatic, and other functions were not employed. The toxic effects of partially purified renin solutions noted by Winternitz, et al.,²⁴ and Leiter and Eichelberger²⁵ are probably related chiefly to their employment of the intravenous route. All of our injections were given intramuscularly. Moreover, the toxic substances demonstrated by Winternitz and Leiter in their partially purified kidney extracts are not necessarily related in any way to the

prophylactically and therapeutically potent principle or principles in the renal extracts which we have employed.

In order to ascertain the active principle or principles in these renal extracts, we must conduct studies on larger groups of dogs, treated prophylactically and therapeutically with partially purified renin solutions and with highly purified renins. The effect of dosage, which has been briefly investigated in some of the therapeutic experiments reported above, as well as the effect of route of administration, must also be studied further. These investigations are in process.

If future results substantiate the continued promise of our observations to date, we shall study the effect of this type of treatment in essential hypertension in man.

CONCLUSIONS

1. For the first time, experimental renal hypertension was prevented in six of fifteen dogs by the daily intramuscular injection of certain partially purified renin solutions for three months before, and three months after, constriction of the renal arteries. Two of four dogs were protected by hog renin, one of four by heat-inactivated hog renin, two of four by dog renin, one out of one by rabbit renin, and none of two by inactive human renin.

2. Liver extract, prepared like partially purified renin, offered no protection to three dogs; all of sixteen untreated control animals developed experimental renal hypertension after constriction of the renal arteries.

3. Daily intramuscular injections of partially purified hog renin solution for four months or more produced striking reductions in the blood pressure of renal hypertensive dogs. Three of four animals showed therapeutic responses to a second course of hog renin equal to the excellent effects which resulted from a course of hog renin administered one year before. One dog which had previously received a course of inactivated hog renin, and one that had previously been given dog renin, without antipressor effect in both cases, showed reductions in blood pressure to normal levels during a subsequent course of hog renin.

4. The mechanism of these prophylactic and therapeutic effects is not now apparent. They may be due to renin or to some other substance or substances in the partially purified renal extracts. Antirenin is almost certainly not involved.

5. Attempts to identify the active principle or principles in the renin solutions and to clarify the mechanisms involved are being made.

We are grateful to R. E. Vessey and V. Miszeika for technical assistance.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

I. FACTORS WHICH AFFECT ITS DIRECTION AND ITS RELATION TO THE MEAN QRS AXIS

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WITH AN APPENDIX ON NOTATION BY R. H. BAYLEY, M.D.†

IN 1934, Wilson, Barker, Macleod, and Johnston¹ published an important paper dealing with the areas of the ventricular deflections of the human electrocardiogram. It was shown that the net area of the QRS-T, above or below the isoelectric line, in any two limb leads, could be used to calculate the direction and magnitude of the manifest area of QRS-T. Since it possesses both direction and magnitude, this quantity is a vector and was called the ventricular gradient by Wilson, Macleod, and Barker.² The papers cited give a fairly detailed explanation of the QRS-T vector, and to them the reader is referred. It will, therefore, be sufficient here to give a briefer explanation.

1. THE NATURE OF THE VENTRICULAR GRADIENT

Fig. 1 shows a sphere of cardiac muscle, lying in a saline solution at the center of an Einthoven triangle. The points in the solution, labeled RA, LA, and LL, are at the corners of the triangle and are equidistant from the muscle. Each pair of points is connected to a galvanometer, in the same fashion as the limb leads are connected to the extremities in human electrocardiography. The three leads will be called Leads I, II, and III. While recording the three leads simultaneously, a stimulus is applied to the surface of the sphere at S. The wave of excitation, thus initiated, progresses through the muscle from the reader's left to the right. During the time of its passage, point RA is negative, point LA is positive, and point LL is, on the average, at zero or earth potential. (Papers which give the experimental evidence for this and other statements in this section are quoted in a textbook.³) Consequently, an upward deflection, R, is seen in Lead I, an upward deflection, R, of half the height, in Lead II, and a downward deflection, of the same amplitude as R₂, in Lead III. These waves, like the QRS complex of the human electrocardiogram, are a result of the passage of the wave of depolarization through the muscle. When recorded on the film it is possible to ascertain the area of each wave in microvolt-seconds (m.v.s). With the usual standardization, and time lines 0.04 seconds apart, a potential of 0.1 millivolt, acting upon the galvanometer for 0.04 second, gives a

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small, rectangular deflection of just the size of one of the small time-potential rectangles recorded on the film. This rectangle has a value of 4 m.v.s. Because it is convenient, and obviates one source of error, we have not converted our measurements of area to m.v.s., but refer to each rectangle as a unit of area. We will suppose, for purposes of discussion, that the R wave in Lead I, as recorded from the sphere of muscle, has an area of 10 units. Since the R is upright, we may call it positive, and its area is +10 units. In Lead III, the area of the deflection is -5 units, just half the area of R₁ and opposite in sign. These two quantities, +10 and -5, may now be used to ascertain the direction of the mean axis of this initial deflection. In this example, the direction is 0°, that is, from left to right and parallel to the line of Lead I.

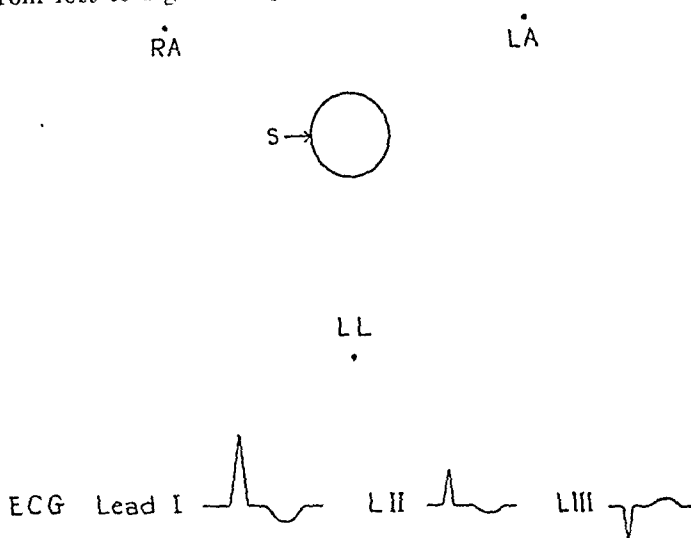


Fig. 1.—This is discussed in the text.

After depolarization of the muscle, repolarization begins. In a physiologically uniform muscle, the area, although not the shape, of the T is the same as the area of the initial deflection, R, but its direction is opposite. In Lead I, the area of the T is -10 units, and, in Lead III, +5 units. The direction of the vector representing T is just opposite to the direction of the R, namely, $\pm 180^\circ$. If we add algebraically the areas of the initial and the final deflection in each lead, we will have the net area of the whole diphasic curve, or, in man, the net area of the QRS-T complex. In our experiment, in each lead the algebraic sums are zero. The gradient of the muscle is zero in magnitude and, consequently, has no direction.

Everyone knows that in the normal human ventricular electrocardiogram the net areas of the QRS complex and the T wave in any lead are neither characteristically equal, nor are they opposite in direction. This means, most probably, that the sequences of depolarization and repolarization in man's ventricles are not the same but, usually, about opposite. The result is that the average mean electrical axis of the

QRS complex in man is nearly $+60^\circ$, and, of the T wave, only about 10° or 12° to the left of this.

Returning to the muscle sphere, it is experimentally an easy matter to reverse the direction of the T wave. All we need to do is to cool the left half of the sphere sufficiently, while keeping the right half uncooled. A stimulus is now applied to the muscle, as before. We will assume, contrary to fact, that the cooling does not change the velocity of the wave of excitation. The initial deflections are then precisely like those derived from the uncooled muscle. In this case, however, the cooled half becomes repolarized much more slowly than the uncooled half of the muscle. Consequently, the right half, which is last to be activated, is now first to recover. The electrical effects of repolarization are reversed, and the T waves are in the same directions as the initial deflections in all leads. If the cooling was just sufficient to produce a T wave of the same area as the R, the net area of R-T, namely QRS-T, in Lead I is now $+10 +10$, or $+20$ units, and, in Lead III, -5 and -5 , or -10 units. The gradient has a magnitude of 20 units, and a direction of 0° , in this case.

If the upper half of the muscle were cooled instead of the half surrounding the point of stimulation, and cooled to the same temperature as before, the resulting gradient would still possess a magnitude of 20 units, but it would point straight downward, i.e., its direction would be $+90^\circ$, and at right angles to the direction of the initial deflection.

As we have pointed out, if the sequence of repolarization is the same as that of depolarization, there is no gradient. It is evident, therefore, that the gradient is an expression of those electrical forces which appear when the sequence of repolarization differs from the sequence of depolarization. It may be noted in passing, and this is an important point, that diminution in T-wave amplitude, and even reversals in the T-wave direction and in the electrical axis of the T wave, can result from a mere diminution in the magnitude of the gradient, and may occur under a variety of purely physiologic, as well as pathologic, conditions.

It is possible to record directly the areas from which the gradient is derived. For example, the stimulus may be applied at the geometrical center of the sphere of muscle. The wave of excitation spreads outward in all directions, but the galvanometers record nothing because each electrical force is balanced by an opposing one. No initial deflections appear. But, on repolarization, the uncooled half of the muscle, i.e., that on the left in the figure, becomes repolarized more rapidly than the cooled half, and a large T wave is inscribed in each lead. In Lead I, the area of the T wave is $+20$ units, and, in Lead III, -10 units, that is, the areas previously derived by adding the areas of the initial and final deflections. The gradient, thus derived, again has a magnitude of $+20$, and its direction is 0° . It makes no difference where we stimulate the sphere, on the inside or on the outside; the gradient remains unaffected, as the experimental results of Wilson,

Barker, Macleod, and Johnston¹ demonstrated. Furthermore, the time required for passage of the impulse through the muscle will not affect the gradient. Let us suppose that we can cause exactly a 50 per cent increase in the time required by the impulse to invade the muscle in the example of the partly cooled muscle, and again stimulate at S. The R wave in Lead I, since it is twice as wide as before, now has an area of +20, and the net area of the T wave is zero. In Lead III, the area of the initial wave is -10, and the T wave has an area of zero. Similarly, in the human heart, in the two cases of partial bundle branch block in which we have made measurements, the change in intraventricular conduction time from no block to block caused no change in the size or direction of the gradient beyond the limits of error in measurement. There is little change in the gradient in ventricular premature beats, and the change is probably a consequence of the prematurity and the resulting alteration in physiologic state when the early beat occurs.

The ventricular gradient is the fundamental quantity in electrocardiography. A change in the gradient reveals a change in the state of the muscle, as Wilson has emphasized. All T-wave changes which are unassociated with QRS complex changes are caused by changes in the state of the muscle, as in our first example of the cooled muscle. Other T-wave changes are like those in some cases of bundle branch block, and are related to QRS change and not to muscle change. In other cases, both factors operate. It is important to make the distinction; this Wilson has also stated.

2. MEASUREMENT OF THE VENTRICULAR GRADIENT

One thing which has inhibited study of the gradient is the opinion that, unless special methods are employed, its cursory measurement is too inaccurate to be valuable. It is to be noted in this connection that slightly inaccurate quantitative estimations may be vastly preferable to no measurements at all, just as the palpatory method of estimating blood pressure was better than none. There are two things that we wish to know about the gradient, namely, its magnitude and its direction. We find that in most cases the former can be estimated with an error of less than ± 10 or ± 15 per cent, and the latter with an error of not over ± 4 or ± 5 degrees. With enough practice, two observers can agree within those limits in the majority of cases. Certain types of records cannot be measured with this degree of accuracy. If the net area of the QRS vector is less than about 4 units, the error in estimating the direction increases, and the error is, in general, inversely proportional to the size of the vector. In this case, even though the percentage error in estimating vector size is large, this is unimportant, for the practically important question is to know whether the vector is small or not. In estimating the size and direction of the gradient, the chief error comes from inaccuracy in placing the base line of the T wave, and particu-

larly in making proper allowance for the magnitude of a normal deviation of the S-T segment, which has been taken as a part of the net T area.

We examine the electrocardiogram with a good reading glass. Following a schema used by Dr. R. H. Bayley, we often estimate the area of an R wave by multiplying its height by half its base, but extreme care must be taken in estimating the width of the base and in allowing for curvature of the ascending or descending limbs. One must also guard against an optical illusion. When an R wave is split by a time line, its ascending and descending limbs appear to be concave; when the R lies between two time lines, its limbs tend to appear convex. The eye also tends to make the base of an R wave which lies between two time lines exactly equal to the time between the lines, although the actual width of the R may be slightly greater or less. These remarks also apply to other waves of good amplitude. The area of R is the area contained within its boundary lines and above the level of the P-R segment at the lower edge of the string shadow. The area of Q is analogously derived, with reference to the upper edge of the P-R segment. The area of S is the inside area below the upper edge of the S-T junction, or, if that junction is deviated, below the level of the base line between T and P, or U and P, if a U is present. The Q and S areas, as negative quantities, are subtracted from the area of R, as a positive quantity, to give the net area of the QRS. The area of T is the net area of any S-T segment shift which may be present and of the T wave proper, so-called. Considerable errors may occur in measuring the T, unless the U-P segments of the cycle before and after the T rest precisely on a horizontal line. Since this condition is not usual, we often measure the apparent areas of two T waves, the base of one which is slightly above, and the base of the other, slightly below, a horizontal millimeter line. The estimate for the one T may, for example, be 5.3 units; for the other, 7.2 units. If the base of one T is apparently just as much below the base line as the other is above, we will be close enough if we call the area 6.2 units. Differences of 0.4 or 0.5 unit in areas of this magnitude have a surprisingly small effect upon vector direction and an unimportant effect on vector size. In those cases in which the net area of QRS in Lead I or in Lead III (which are the leads we use) is nearly zero, and the areas in the other lead are relatively, although not necessarily absolutely, large, the error in estimating the direction of the QRS axis should not be over 1° . One should, of course, make sure that standardization is correct, and, if not, make the proper corrections. In recording the measurements, it is convenient to set down, for each of the two leads chosen, the net QRS area, the T area, and the algebraic sum of these two for the net QRS-T area on one horizontal line. The measurements from the other lead are placed on the line below.

Once the net areas are estimated, they are used to ascertain the directions of the vectors. For this purpose the chart devised by

Dieuaidé was used. For estimation of the manifest areas or magnitudes of the vectors, a simple schema is given in Table I. It applies only to vectors derived from Leads I and III.

The directions of the vectors are first ascertained. The following axes are then taken as *bases*, from one of which the axis in question will deviate by 30° or less: 0° , $+60^\circ$, $+120^\circ$, $\pm 180^\circ$, -120° , -60° .

(a) When the net areas in Lead I and III are both positive or both negative, they are added, and the sum is increased by the following percentages, depending upon the number of degrees of deviation of the axis as ascertained from the nearest *base*, as described in the previous paragraph.

TABLE I

NUMBER OF DEGREES BETWEEN BASIC AXIS AND OBSERVED AXIS	PERCENTAGE INCREASE IN PROJECTED VECTOR LENGTH, TO GIVE THE MANIFEST VALUE
30	15.4
29	14.3
28	13.3
27	12.3
26	11.3
25	10.4
23	8.6
20	6.3
17.5	4.8
15	3.6
10	1.5
5	0.4
0	0

For example, if the net QRS areas are of the same sign in both Leads I and III, they are added. Let us suppose their sum is $+7.6$ units. We will further suppose that the electrical axis of the QRS is $+75^\circ$. Now 75° deviates by 15° from the nearest one of the basic axes given above. Hence we add (Table I) 3.6 per cent of 7.6 units to obtain the manifest value of the mean QRS vector. This value is, therefore, 7.8836 units, or, in round numbers, 7.9 units in magnitude. If desired, the figure 7.8836 can be multiplied by 4, giving 31.6 m.v.s. Since the error in measurement is necessarily rather large, it is quite meaningless to employ more than one figure after the decimal place; and, when multiplied by 4, the nearest m.v.s. in value is usually close enough.

(b) When the net area in one lead (I or III) is positive and in the other lead (III or I) is negative, the two are not added, but the value of the largest net area (neglecting its sign) is increased just as in case (a). Suppose that the net area in Lead I is $+10$ and that, in Lead III, it is -8 . The direction is then -20° . This deviates by 20° from 0° , the nearest of the basic axes, as we have called them. In this case the larger value, 10, is multiplied by 106.3 per cent of itself. The manifest value is, therefore, 10.6 units. If the angle happens not to be one given in the table above, one can easily interpolate.

3. THE NATURE OF THE MATERIAL USED

The electrocardiograms used in this study were from 277 persons. The results, which are shown graphically in Fig. 2, were also supported by less careful measurement of about 200 additional electrocardiograms from patients without heart disease. About 50 of the 277 electrocardiograms were from medical students and other normal subjects. The remainder were from patients who, judging from routine hospital examination, were regarded as having no heart disease. Thus it cannot be asserted that all of the patients, particularly the older ones, were without heart disease. A few of our divergent points in Fig. 2 may have come from patients of doubtful cardiac normality. It will become clear, however, that this possibility can have no influence whatever on the correctness of our conclusions, particularly because some of the most discordant points in the figure were from normal controls. Few records from patients over 45 years of age are included. Most of the records were taken with the subject in the recumbent position, but a small number were seated, and one, discussed later, was standing. Electrocardiograms from patients with fever or thyrotoxicosis were excluded. In addition, but not reported in this paper, measurements of the electrocardiograms of several hundred patients with heart disease were made.

Over 200 electrocardiograms were selected at random. The remaining records were chosen because they showed extreme QRS axis deviations for apparently normal subjects. This explains the relatively large number of QRS axes below $+10^\circ$ and above $+90^\circ$. The proportion shown in the figure would not hold for a purely random sample.

Different records were recorded by means of any one of four string galvanometers used by Charity Hospital or the medical school. The standardization was usually correct. When it was not, the appropriate correction was made, e.g., if 1 mV gave a deflection of 11 mm., the size of the measured area was reduced by 9 per cent, or one-eleventh.

4. FACTORS INFLUENCING THE DIRECTION OF THE NORMAL VENTRICULAR GRADIENT

(a) *Rotation of the Heart About Its Anteroposterior Axis.*—One of the most important of the factors which determine the direction of the ventricular gradient is the position of the heart in the thorax, with reference to its rotation around its anteroposterior axis. This can best be judged by a comparison of the gradient and the heart as seen in the roentgenogram.⁶ For purpose of definition, and because the terms are established in the literature, we shall speak of clockwise rotation about the anteroposterior axis as rotation to the *right*, and the reverse direction as rotation to the *left*, even though we recognize that the names are illogical. At this time, we cannot make a detailed statement of the relationship between the gradient and rotation to the right or left, but

we can make a few general statements. The gradient of the vertically placed heart is relatively vertical, i.e., usually between $+60^\circ$ and $+80^\circ$. It is usually more vertical than is the apparent longitudinal anatomic axis of the ventricles. As we shall see, this lack of close correspondence between the anatomic and electrical axes is attributable to the usual rotation of the vertically placed heart about a longitudinal axis. In contrast, the gradient of the transversely placed heart lies much farther to the left than the gradient of the vertical heart, but, again, the correspondence between apparent anatomic axis and electrical axis is not usually precise, and for the same reason. The gradient of the transverse heart is often more transverse than the anatomic axis. It follows that the range in the direction of the gradient is greater than the range in the direction of the anatomic axis, and this difference in range is even more pronounced in the case of the QRS axis. However, these facts must not be taken to mean that the directions indicated by the mean electrical axes deviate greatly from their true directions as these are projected on the frontal plane.

(b) *Rotation of the Heart About a Longitudinal Axis.*—As long ago as 1925, it was shown by Meek and Wilson⁴ that rotation of the heart about its long axis produced a marked effect upon the electrocardiogram of the dog. In general, the effects found by them appear to be similar to the effects of rotation of the human heart. For purposes of definition, rotation of the heart about its long axis in a clockwise direction as the heart is viewed from the apex will be referred to as clockwise rotation; and rotation in the opposite direction will be designated counterclockwise rotation. Human hearts which are placed vertically in the thorax are known from anatomic studies usually to be rotated more or less in a clockwise direction, and the majority of such hearts show an S and no Q wave in Lead I, and a Q wave and a small or no S in Lead III. A QRS complex configuration of such a type, whether observed with a vertical or transverse heart, we shall regard as an example of clockwise rotation. In contrast, many transversely placed hearts, as compared with vertical hearts, are known to present a larger area of left ventricular surface when viewed from the front. The electrocardiogram in such cases typically shows a Q wave and no S wave in Lead I, and an S wave and no Q wave in Lead III. We shall regard such electrocardiograms as evidencing counterclockwise rotation. Other electrocardiograms, not quite typical of either type, do, however, betray, fairly clearly, rotation in one direction or the other. Absence of a typical Q wave is the most frequent feature of this group of records. Still other electrocardiograms can be placed in neither group, or show characteristics of both groups. Most of these can be classified as examples of no rotation about a longitudinal axis. Some records show a Q_1 and an S_1 and an M complex in Lead III. This usually means counterclockwise rotation, although, when the middle

portion of the M is shallow, the rotation may be slight or absent. Certain other records show an S wave in the three leads, but no Q waves; or a Q wave in the three leads and no S waves. How these should be classified will be stated below.

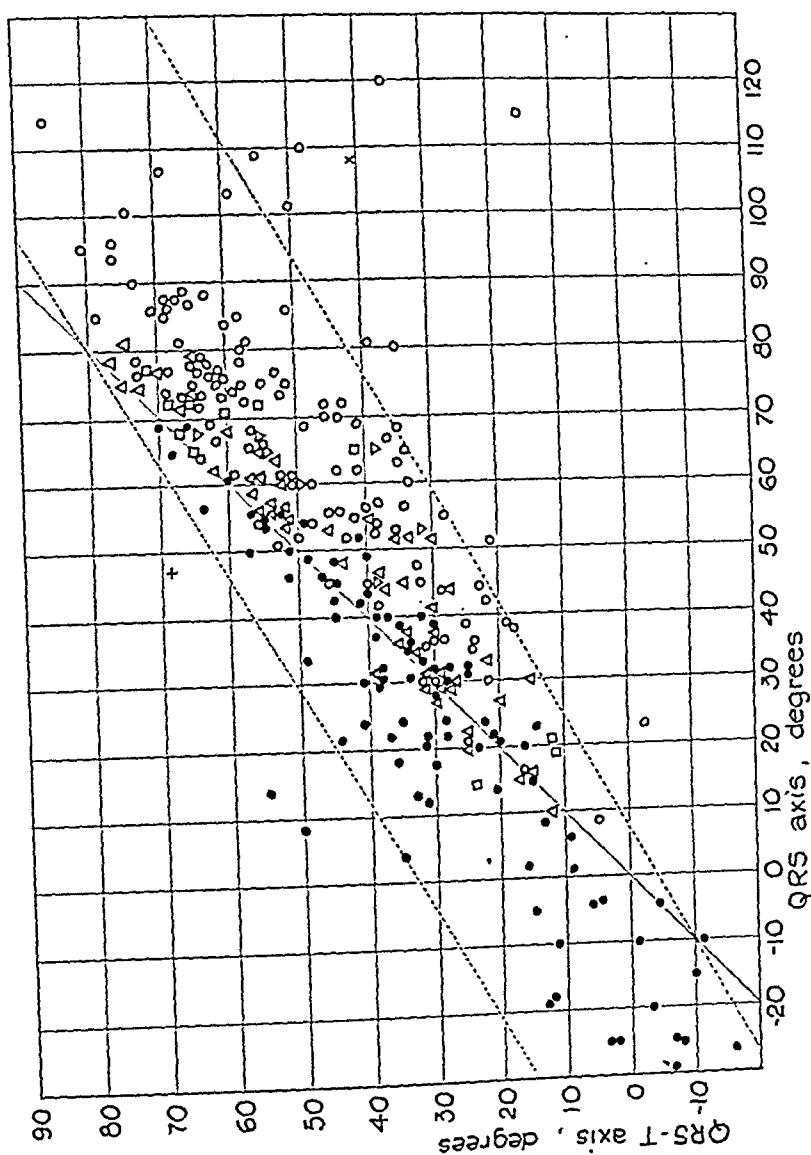


Fig. 2.—The relation between the mean axis of the QRS complex and the direction of the gradient, or the mean axis of QRS-T. As evidenced by the form of the QRS complexes, the hearts corresponding to the open circles were rotated clockwise; to solid circles, counterclockwise; to Δ , no rotation. For meaning of the other points, see text.

In Fig. 2, the average QRS axes are plotted against the directions of the ventricular gradients. Each of the 122 points represented by an open circle is from a case in which the electrocardiogram indicated clockwise rotation. It will be observed that, when the QRS axis is above $+60^\circ$, not one of the gradients lay farther to the right than the QRS axis of the same heart, and all but one lay to the left of the QRS axis. When the QRS axis is below $+60^\circ$, a few of the gradients lie to the right, although a majority still lie to the left of the QRS axis. It may be stated that when the electrocardiogram of the normal heart shows clockwise rotation, unless this rotation is extreme, the ventricular gradient rarely lies more than 5° to the right or more than 35° to

the left of the mean QRS axis. Sinus tachycardia was present in the large majority of cases in which the gradients approached the 35° limit.

In contrast, the 87 points represented by solid circles are examples of counterclockwise rotation, according to our criteria. In these cases, the gradient rarely lies more than 32° to the right, or more than 10° to the left of the QRS axis.

More interesting are the fifty-three points indicated by a delta. These are electrocardiographic examples of little or no rotation. With only two exceptions, their gradients lie within a narrow band, ranging from 5° to the right, to 17° to the left, of the QRS axis. The narrow range of deviation between the gradient and the mean QRS axis, amounting to only 22° , is, we believe, of considerable significance, particularly when we recall that not all of these hearts can be regarded as being strictly nonrotated. This observation suggests that, with few exceptions, the gradient and the mean QRS axis bear a close relation to each other in normal hearts. Furthermore, this fact, together with the ranges for the rotated hearts, strongly suggests that the electrocardiographic criteria for rotation are fairly reliable, although more remains to be done in establishing the kind of rotation in certain electrocardiogram types. In unpublished studies, using a different approach, Dr. Manuel Gardberg and one of us arrived at precisely the latter conclusion. It must be repeated here that this conclusion is quite independent of the further question as to whether or not the directions of the axes, as recorded, are their true directions.

There remain on the chart eleven points indicated by squares, and seven indicated by inverted deltas. The squares represent records in which there was an S wave in all three leads, with little or no Q wave in any lead, and with R_2 higher than R_1 . The distribution of the points suggests that these hearts are relatively unrotated, or slightly rotated in a clockwise direction, although another interpretation is possible. The inverted deltas represent electrocardiograms that showed a Q, and no S, in each of the three leads. The distribution of the points suggests clockwise rotation.

There are 9 points for hearts rotated in a clockwise fashion whose gradients lie much farther to the left of their QRS axes than 35° . The five instances with a QRS axis of more than 90° are electrocardiographic examples of extreme clockwise rotation. The significance of their position is taken up in the discussion.

In 1937, Ashman and Hidden⁵ published a paper on rightward deviation of the T-wave axis as an index of myocardial disease. Rightward deviation of the T wave is, of course, usually associated with similar deviation of the ventricular gradient. It is interesting to find that the results of that study, which was purely empirical, agree well with the limits of deviation of the gradient relative to the QRS axis, as reported herein. In that study it was tacitly assumed that hypertrophy of the left ventricle, sufficient to rotate the T wave abnormally

to the right, signified disease. That point of view is debatable. In any event, such hypertrophy is not normal, and disease is potential, if not present. For reasons which will be taken up in the second paper of this series, abnormality of the gradient should prove a much more reliable and consistent indication of disease than the T-wave amplitude or direction.

Bayley, Holoubek and Baker⁶ concluded, from measurements of the gradients of 100 normal hearts, that, in patients with normal QRS complexes, the gradient should not lie more than 24° to the right of the QRS axis, nor more than 35° to the left of it. We have extended the total range as given by them, but, at the same time, we have narrowed it by suggesting separate narrower ranges for hearts differently rotated on their long axes.

In a later paper we shall consider the effects of disease on the gradients and the means of making proper correlations between the gradient and the QRS axis. For the present it may simply be pointed out that nonrotated hearts have gradients which range only slightly to either side of the QRS axis; that the gradients of clockwise rotated hearts range farther to the left, and that there is some correlation between the electrocardiographic evidence of degree of rotation and degree of deviation between the two axes; and that the gradients of the counterclockwise rotated hearts range to the right of the gradients of nonrotated hearts.

It is important to note that the relation between the QRS axis and the gradient, as outlined above, is valid only for hearts in which there is no defect or anomaly in intraventricular conduction. When the mean QRS axis changes as a result of such factors, the gradient, providing there is no myocardial change, remains unaffected, both in magnitude and direction.

(c) *Rotation of the Heart About Its Transverse Anatomic Axis.*—It is well known that the longitudinal anatomic axis of the heart not only points downward and to the left, but is also directed forward to a greater or lesser extent. In persons with short anteroposterior thoracic diameters, the heart must be relatively vertical. Such a heart may be regarded as one, the apex of which is swung downward or the base upward. When the anteroposterior diameter is large, the valve openings are likely to be farther behind the anterior chest wall; the apex can be regarded as having swung forward and upward. We have not yet made a systematic study of the effect of this rotation upon the electrocardiogram, but there is good reason to suppose, as we shall point out in the discussion, that such rotation has its effect in producing QRS vectors of different magnitudes and in causing unusual degrees of deviation between the QRS axis and the ventricular gradient.

(d) *Posture.*—In eighteen of a series of twenty-three cases, nineteen of our own, and four from Scherf and Weissberg,⁷ a change from recumbency to the standing position caused the QRS axis to deviate to

the right. In five cases there was either no change or a slight shift to the left. The ventricular gradient shifted to the right in eleven of the twenty-three cases, and to the left in twelve cases. Without exception, the size of the gradient was diminished. In ten cases the size of the QRS vector was increased and in thirteen cases it was diminished by standing.

(e) *Heart Rate and the Direction of the Gradient.*—In too large a number of cases for it to be accidental, we have observed a leftward shift of the gradient, relative to the QRS axis, with sinus or supraventricular paroxysmal tachycardia. The reason for this shift is obscure, although it is correlated with depression of the S-T segment in Lead III, and it may be related to a change in cardiac position during systole. Its extent is not great, as a rule. The four points in Fig. 2 which represent QRS axes of less than 90° , and gradients well to the left of the QRS, are from persons with sinus tachycardia, except one, who had paroxysmal tachycardia. The majority of the persons with slightly lesser gradient deviation also had rapid hearts.

That it is not the tachycardia itself, but a change associated with tachycardia under some, but not under all, conditions that causes a leftward shift of the gradient was shown by a study of six persons to whom amyl nitrite was administered. The increase in heart rate averaged 35 beats a minute, and ranged from 23 to 55 beats. In one person the gradient appeared to swing 8° to the right, but this effect was illusory, and was clearly caused by slowing of the heart between the taking of Leads I and III. In three others, also, the direction was essentially unchanged. In the other two persons, an apparently significant change was clearly related to a change in respiratory level. Although the number of cases is small, it can be stated that acceleration of the heart brought about by amyl nitrite inhalation has little, if any effect upon gradient direction in recumbent, normal subjects.

5. DISCUSSION OF RESULTS

(a) *The Significance of the Relation Between Rotation on the Heart's Long Axis and the Angle Between the QRS Axis and the Gradient.*—We have noted that the gradients of hearts which are rotated clockwise around an axis which is close to the long anatomic axis point to the right of the anatomic axis, but to the left of the QRS axis. On the other hand, when the heart is rotated counterclockwise the gradient points to the left of the longitudinal anatomic axis, but to the right of the QRS axis. These relationships are so consistent that they can mean only one thing, as reference to Fig. 3 will show. The longitudinal axis of rotation points somewhat forward, downward, and to the left, as anatomic considerations suggest. The gradient axis points less far forward. It lies behind the longitudinal axis of rotation. Hence, when there is clockwise rotation of the heart, the tip of the gradient swings to the right, and vice versa. The QRS axis, in turn, lies behind the

gradient, so that, on clockwise rotation of the heart, it points farther to the right than does the gradient, and, consequently, the gradient points to the left of the QRS axis. On counterclockwise rotation of the heart the reverse changes occur. The QRS axis swings farther to the left than the gradient, so that the latter now points to the right of the QRS axis. We have already given our criteria for rotation of the heart on its long axis. We have checked the criteria against a considerable number of roentgenograms and electrocardiograms in Master's very useful book⁸ and by means of a few fluoroscopic examinations; the consistency of the relation is very good. A later paper will deal in detail with the relation of the electrical axes to the anatomic axis.

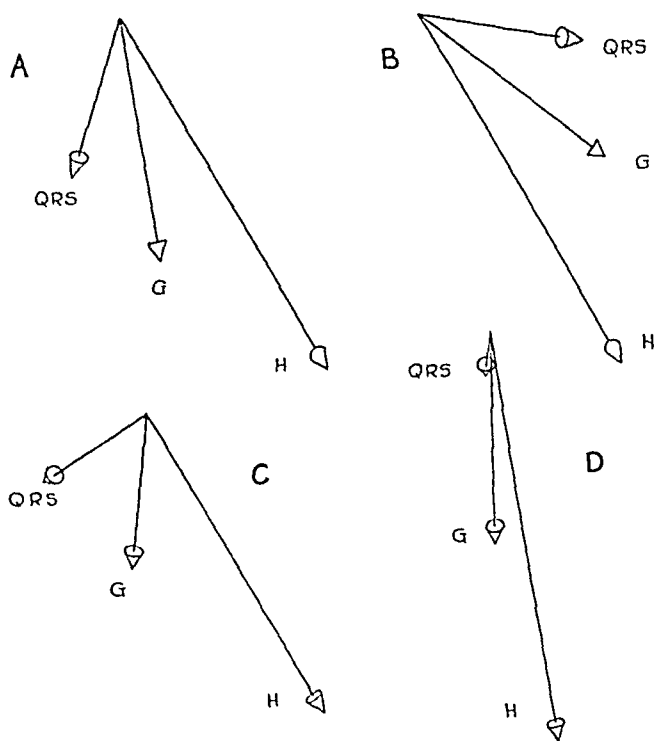


Fig. 3.—H represents a longitudinal axis of rotation of the heart. The G is the gradient, here represented as shorter than H. (Since H is not a vector, it has no length comparable to the length of G and Aqrs). QRS is the mean axis of the QRS complex (SAqrs), and in absolute length in our model (though not as projected) was about 85 per cent as long as SG.

The actual angle between H and G has not yet been accurately calculated. Therefore, the angle shown by the model, 35°, is merely for illustrative purposes.

The effect of changes in position, and of rotation about H, upon the angles can be mathematically ascertained. The diagrams, however, are taken from the shadow of the model, projected upon a white screen representing the frontal plane. The plane of the paper of this page is the frontal plane.

A represents a moderately vertical heart, rotated markedly in a clockwise direction (see text). The alpha angles of G and QRS correspond roughly to the point at the upper right corner of Fig. 2.

B is the same heart, rotated markedly counterclockwise. This approximates the first case discussed in section 5 c, although that heart was somewhat more transverse, and the rotation, though unusual for the heart position, not quite so great.

C shows the same heart, with the apex pushed back markedly. Note the effect upon the length of the vectors and upon the size of the angles. This position hardly ever occurs in normal chests.

D shows a very vertical heart, with only slight clockwise rotation; the apex is pushed back. The anatomic axis (not shown) still projects forward slightly. Fore-shortening has greatly reduced the manifest area of QRS, but has less effect on the gradient, which lies in front of QRS. No point in Fig. 2 quite corresponds to this position. The QRS axis is at +100°, and the gradient at +90°.

(b) *The Size of the Angle Between the QRS Axis and the Gradient.*—This question will be considered in a later paper. Since rotation of the heart which we have designated clockwise or counterclockwise is about an axis which is possibly not identical with the longitudinal anatomic axis of the heart, the problem in question can be solved only after this axis of rotation has been considered. The rotation is not about the QRS axis, nor about the gradient. It can be said, however, that the angle between the QRS and QRS-T axis is approximately 25° to 35° , on the average.

(c) *Discussion of Exceptional Cases.*—We may anticipate the later report in order to discuss a few of the cases represented by points in Fig. 2. Reference to the diagrams in Fig. 3 shows that rather moderate rotation of the heart about a longitudinal axis will enable us to explain the rotations in the usual ranges, as they have been given. In two of the unusual cases fluoroscopic examination was done. One is shown twice in Fig. 2; the measurements from two separate electrocardiograms, taken at different times, are given. The points are those at a QRS axis of $+4^{\circ}$ and a QRS-T of $+35^{\circ}$, and at $+8^{\circ}$ (QRS) and $+50^{\circ}$ (QRS-T). The person was a healthy medical student of sthenic habitus, tending toward hypersthenic, whose record showed the same peculiarities a year previously. His thorax was not abnormal in form and the heart was of normal size and in about the average position for his build. The pulmonary conus showed no prominence. Lateral and oblique views showed no peculiarities. His blood pressure was normal. His electrocardiogram, to be published in the second paper of this series, revealed a low T_1 , a much higher T_3 , and "left axis deviation." The waves R_1 and S_3 were of normal amplitude and the net manifest area of the QRS complex was 5.1 units (see section 1), in contrast with the average area for males of 6.7 units. There was, therefore, no electrocardiographic suggestion of hypertrophy. According to Ashman and Hidden's⁵ work, the ratio T_1/T_3 was abnormal. Yet, to explain this unusual observation, all we need to assume is that the heart was rotated about 10° or 15° more in a counterclockwise direction than is common for a heart in this position. The angle between the QRS and the gradient for his second point (referred to in Fig. 2) is 42° . This angle is rather large, but may be explained either as the result of foreshortening caused by projection on the frontal plane, or to a real, although slight and unusual, deviation between the axes. On standing up, this subject's axes became 30° (QRS) and 43° (QRS-T), which is a common relation. A very slight change in the position of the heart can account for the differences in the two records which were taken in the supine position, but a 10 or 20° rotation clockwise around a long axis must be assumed to explain the difference between recumbency and standing.

The other atypical record from a patient who has been examined fluoroscopically is the point in Fig. 2 at $+109^{\circ}$ and $+55^{\circ}$. In this case

the person was seated. As in the other case, we are indebted to Dr. James L. Gouaux for the fluoroscopic examination, which we witnessed. The person, employed by the hospital, is a healthy, young, colored woman of slender build. The anteroposterior diameter of her thorax is distinctly small, although there is no deformity. In the anteroposterior view the heart appeared somewhat enlarged, with a slight convexity of the pulmonary conus region, and not vertical. The angle between the horizontal and a line drawn from the angle between vena cava and auricle to apex was about 50° . Oblique and lateral views demonstrated that there was no actual cardiac enlargement. The net manifest area of the QRS complex was 3.1 units, in contrast with an average for women of 5.9. When the electrocardiogram was taken, the heart rate averaged 100/min. It showed rather marked "right axis deviation" and clockwise rotation. When, as in Fig. 2, we place the anatomic axis at 50° , push the apex back a few degrees to fit the flat chest, and rotate the heart clockwise, we quite readily reproduce the record as observed, except that the gradient is about 15° too far to the left. But since, when the heart rate is rapid, we often observe a shift of nearly this order of magnitude, we may say that the fluoroscopic observations quite satisfactorily fit the electrocardiogram. The QRS manifest area is small because of foreshortening of the QRS axis.

The point at $+114^\circ$ (QRS) and $+86^\circ$ (QRS-T) was from a rather slender, flat-chested medical student who was standing when the record was made. In the recumbent position, the axes were at $+86.5^\circ$ and $+75^\circ$. The manifest area of the QRS was 7.6 in both positions. In spite of the relative flatness of the chest, the clockwise rotation of this subject's heart prevented marked foreshortening of the QRS axis. Hence, as projected on the frontal plane, the area of QRS was not small, and the angle between the QRS axis and gradient was not unusually large.

The point at 115° (QRS) and $+15^\circ$ (QRS-T) was from a tall, but heavy-set and rather obese, man, about 35 years of age. His blood pressure was variable, sometimes going as high as 190 mm. Hg, systolic. Hence, myocardial changes might be held responsible for the abnormalities, but they can be explained without that assumption. His heart rate was 115/min. Two other records, the last taken nineteen months later, showed no change. His electrocardiogram can be explained by assuming a very transverse heart, together with clockwise rotation, and a longitudinal axis of rotation which almost parallels the anterior chest wall. This assumption would necessitate a very small net area of the QRS, and, in fact, the area was only 1.4 units (the average is 6.7). We can assume that here we are dealing with a gradient which is greatly deviated by the tachycardia, but this can produce only a small part of the angle of 100° between the two axes. Perhaps the only unusual feature of this electrocardiogram is clockwise rotation, in the presence of a transverse heart.

The point marked X in Fig. 2 was from a case of pulmonary embolism. Both the QRS and T wave, and, therefore, the gradient, changes are those of marked clockwise rotation of the heart. It is obviously unnecessary to invoke any cause other than rotation and tachycardia to explain the more characteristic electrocardiographic changes which occur in this condition.

The point marked + is from a case, in the literature, of a middle-aged subject who had an attack of coronary thrombosis and died soon after the electrocardiogram was recorded. The record was interpreted as being quite normal. Actually, by the criteria of Ashman and Hidden, it was borderline. As a result of our present study we can say that the record was probably abnormal, for the QRS complexes revealed only a slight counterclockwise rotation and the heart rate was moderate. The first of our normal subjects, discussed above, revealed far more marked rotation.

Finally, three electrocardiograms were not included in the figure because their points fell far outside the range of the QRS axes shown. One, a 48-year-old man, was typical of the group. He had a QRS axis at -90° and a gradient at $+66^\circ$. The manifest area of the QRS was 1.5 units, and, of the QRS-T, 8.5 units. There was an S wave, and no Q, in all three leads. S_1 had the same area as R_1 , and S_2 was larger than R_2 . Another subject, a slender medical student, complained of tachycardia. Examination revealed no evidence of heart disease. His QRS axis was -96° , and its manifest area, 2.3 units. His gradient was at $+75^\circ$ and was of normal size, taking into account the heart rate and small QRS area. On standing, his QRS shifted to -107° , and the gradient to $+51^\circ$. He has suffered from bronchial asthma. Records such as these can also be explained but will be reserved for a later paper.

(b) *The Significance of the Distribution of the Points in Fig. 2.*—We have withheld a consideration of the peculiar distribution of the points in Fig. 2 until the discussion in the foregoing section could give the reader a general idea of the causes of the normal deviations between the QRS and QRS-T axes. It will be noted that the farther to the left the QRS axis lies, the less far is the gradient likely to lie to the left of the QRS axis. We interpret this simply to mean that relatively transverse hearts, for anatomic reasons, are not likely to be rotated far in a clockwise manner. Similarly, the farther to the right the QRS axis lies, the less likely is the gradient to lie to the right of the QRS axis. This evidently means that relatively vertical hearts, for anatomic reasons, are not often rotated much in a counterclockwise fashion. The dotted lines in Fig. 2 show the usual ranges, but points outside these ranges do not necessarily indicate disease.

6. APPLICATION TO ELECTROCARDIOGRAPHIC INTERPRETATION

In general, it may be said that a greater than normal deviation between the QRS and QRS-T axes, for the type and degree of longitudi-

nal rotation shown by the form of the QRS complexes, and not explainable as a result of foreshortening, or by a change in QRS size, as in bundle branch block or ventricular hypertrophy, is to be regarded as indicating myocardial change. It is true that the empirically arrived at criteria now in use are capable, in expert hands, of revealing disease in most instances, but a comparison of current texts shows quite clearly that uniformity in interpretation has by no means been achieved. The need for a more systematic and more rational procedure is obvious. The second paper in this series deals with the other aspect of the gradient, namely, its magnitude. When both the direction and magnitude of the gradient and their relation to the position of the heart in the thorax are considered, more accurate electrocardiographic interpretation should become possible.

SUMMARY AND CONCLUSIONS

The nature of the ventricular gradient is explained. It is the fundamental quantity in electrocardiography. Upon its magnitude and direction, in conjunction with the QRS vector, depend the size and direction of the T wave. Failure to appreciate this fact has tended to thwart efforts to define the normal and abnormal electrocardiogram by empirical methods.

A method of estimating the size and the direction of the QRS and QRS-T vectors is described.

The more important normal factors which determine the direction of the gradient, as projected on the frontal plane, are described and discussed; this was based on a detailed study of the electrocardiograms of 277 subjects, together with less detailed observation of over 200 other subjects.

The normal relation between the QRS-T and QRS vector directions is given and discussed.

A few exceptional individual cases are singled out for special discussion. These serve as an introduction to a later, detailed analysis of the relations between the electrical and anatomic axes, based upon roentgenographic, fluoroscopic, and electrocardiographic study.

Although the implications of our results are suggestive, our observations neither affirm nor deny the importance of tissues of variable electrical conductivity in contact with the heart. To prevent misunderstanding, we do not assert that the directions of the vectors as given in this and in the two following papers are their true directions in three-dimensional space. We do, however, believe that the evidence stresses the fundamental importance of vector analysis in the solution of electrocardiographic problems. We believe, further, that the method will go far to abate the existing chaos in electrocardiographic interpretation, a condition which a comparison of current texts so clearly reveals.

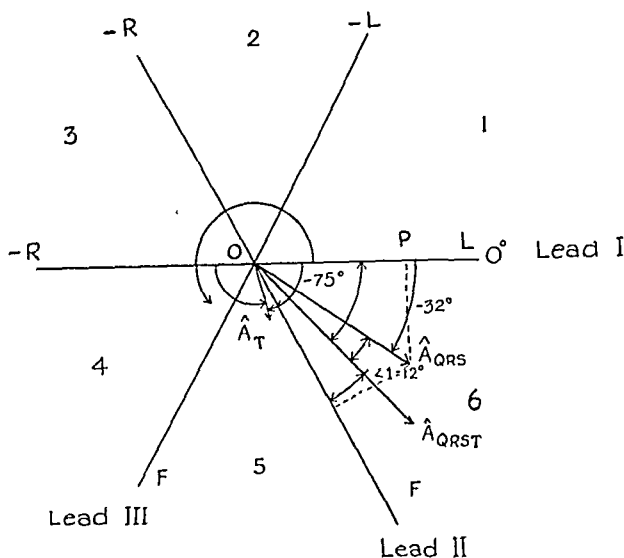
We wish to thank Dr. R. H. Bayley for a valuable critical review of the manuscript of this paper.

ON NOTATION

R. H. BAYLEY, M.D.

Unless a uniform system of notation is adopted, the presentation of material dealing with this important phase of electrocardiography will tend to confuse rather than help the reader. The following notation is therefore suggested:

Let the Einthoven triangle be replaced by its more convenient identity, namely, the triaxial reference system formed by translating the sides of the triangle in such a way that the midpoints of the sides coincide at a common point, the origin O (see Fig. 4). The lengths of the three reference axes are immaterial, and the



OP = area under QRS,

Fig. 4.

axes now divide the frontal plane, RLF, of the body into sextants. Each of the three reference axes, RL, RF, and LF, has a positive and negative half, separated by the origin O. Let the manifest mean axes be denoted as follows:

- \hat{A}_P = manifest mean axis of P,
- \hat{A}_{QRS} = manifest mean axis of QRS,
- \hat{A}_T = manifest mean axis of T,
- \hat{A}_{QRST} = manifest mean axis of QRST.

Here, the letter A indicates that the quantities are determined by the areas under the curves of the electrocardiographic deflections, and the arrowhead indicates that the quantities are vectors. Since the manifest mean axis of QRST is also known as the (ventricular) gradient, we have the identities \hat{A}_{QRST} and G. The motion of these axes is restricted to the frontal plane, RLF. The spacial mean axes, of which the aforesaid axes are projections, generally differ in both magnitude and direction from the manifest mean axes. Therefore, it is suggested that the spacial axes be denoted by prefixing the letter S to the foregoing symbols. Thus,

- $S\hat{A}_P$ = spacial mean axis of P,
- $S\hat{A}_{QRS}$ = spacial mean axis of QRS,
- $S\hat{A}_T$ = spacial mean axis of T, and
- SG = spacial mean axis of QRST or, spacial gradient.

Then, according to custom, the magnitudes of the axes (spacial and manifest) are SA_P , SA_{QRS} , SA_T , SG , and A_P , A_{QRS} , A_T , G , respectively.

The angle made by any two lines radiating outward from the origin O (which designates a common origin for all of the above mentioned vectors) is called a polar angle, and, according to custom, is indicated by writing in brackets the two lines by which the angle is formed. Thus, for the polar angle (1) in the figure, made by \hat{A}_{QRS} and \hat{A}_{QRST} , we have the angle $(\hat{A}_{QRS}, \hat{A}_{QRST})$. In a like manner the polar angle made by \hat{A}_T and the negative half of the Lead I reference axis ($= -RL$) is the angle $(\hat{A}_T, -RL)$. A polar angle may be positive or negative; the sense is determined by the direction, counter-clockwise or clockwise, of measurement. When vectors or when polar angles are positive, it is customary to omit the positive sign. Thus, in the figure, the angle $(RL, \hat{A}_{QRST}) = -45^\circ$, the angle $(RL, -LF) = 60^\circ$, the angle $(\hat{A}_{QRS}, \hat{A}_{QRST}) = -12^\circ$, the angle $(\hat{A}_{QRST}, \hat{A}_{QRS}) = 12^\circ$, etc.

The positive reference axis of Lead I ($= RL$) is customarily taken as the general reference line from which all polar angles are measured, unless otherwise indicated (as in the *aforecited* instances). Thus \hat{A}_{QRS} lies at -32° , and \hat{A}_T lies at -75° , or at 285° , or, less specifically, in that half of the fifth sextant adjacent to the sixth.

The position of any of the spacial mean axes is not defined sufficiently by the position in RLF of the manifest mean axes. Hence, according to widely accepted standards for dealing with like situations, the polar angle made by a spacial mean axis and its related manifest mean axis is described as positive or negative according to whether the shortest motion through which the spacial axis appears rotated out of the frontal plane is counterclockwise or clockwise to an observer stationed at the patient's left. Thus, $S\hat{A}_{QRS}$ and SG (as described in the foregoing article) lie as if rotated through positive polar angles with respect to the frontal plane; the angle $(S\hat{A}_{QRS}, \hat{A}_{QRS})$ is greater than the angle (SG, G) .

The magnitude of a manifest mean axis is always equal to the product of the magnitude of its related spacial mean axis by the cosine of the angle made by the spacial mean axis and its projection upon the frontal plane. For example,

$$G = SG \cos(SG, G).$$

In a like manner, the areas under the curve of the extremity lead electrocardiograms are always equal to the product of the magnitude of the related mean axis (spacial or manifest) by the cosine of the angle made by the limb of the triaxial reference system on which the area is plotted and the magnitude of the mean axis considered. For example,

$$\text{Area } QRS_1 = A_{QRS} \cos(\pm RL, \hat{A}_{QRS}).$$

Using the notation herein suggested, the manifest mean axes have the important relation,

$$G = \hat{A}_{QRS} + \hat{A}_T,$$

or

$$\hat{A}_T = -\hat{A}_{QRS} + G,$$

where the vectors on the right-hand side of these expressions are added by the parallelogram law of adding forces. The negative sign before the vector quantity merely indicates a reversed direction in space. Thus, \hat{A}_T is the directed diagonal (outward from O) of a parallelogram of which $-\hat{A}_{QRS}$ and G form two sides.

Finally, the axis of cardiac rotation, \hat{R} , with origin at O , usually makes a negative polar angle with respect to RLF. When it is desired to describe the position of $S\hat{A}_{QRS}$ and SG with respect to \hat{R} , the normal positions (according to the foregoing article) are such that the polar angles $(\hat{R}, S\hat{A}_{QRS})$ and (\hat{R}, SG) are both positive with respect to \hat{R} , as viewed by an observer stationed at the patient's left. In the frontal plane, left axis deviation becomes positive mean axis rotation, and right axis deviation becomes negative mean axis rotation. When a mean axis deviates away from the normal in both magnitude and direction, the deviation may be referred to as a diversion. When a mean axis deviates towards its normal

value of magnitude and direction, the deviation may be referred to as a reversion. If a mean axis alters its magnitude without changing its direction, the alteration may be referred to as a growth or a decay, according to whether the magnitude increases or decreases.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

II. FACTORS WHICH AFFECT ITS MANIFEST AREA AND ITS RELATIONSHIP TO THE MANIFEST AREA OF THE QRS COMPLEX

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IN THE preceding paper of this series¹ we gave an explanation of the way in which the ventricular gradient of Wilson, Macleod, and Barker² is estimated, with respect both to its manifest magnitude and direction, without, of course, giving its fundamental cause, for that is still unknown. We considered in some detail the relationship between the directions of the ventricular gradient and the QRS axis, and certain of the factors which affect that relationship. The influences which modify the magnitude of the gradient were considered in that paper only to the extent that was necessary to explain the magnitude of the angle lying between the two axes. This paper deals with the factors which affect the manifest area or magnitude of the gradient, and, incidentally, the size of the QRS vector. Of necessity, therefore, it deals with the factors which affect the magnitude and direction of the T wave of the electrocardiogram.

In order to avoid cumbersome verbal repetition, we shall employ certain of the symbols suggested by Dr. R. H. Bayley in his Appendix to the preceding paper. Because certain other symbols or usages are so firmly established, and a complete change would lead to confusion, we have not adopted Dr. Bayley's suggestions in toto. The symbols adopted are the following:

G is the manifest area of the gradient, as projected upon the frontal plane.

\vec{G} is the gradient, considered as a vector, which has both magnitude (namely, manifest area) and direction, as projected upon the frontal plane.

A_{QRS} is the manifest net area of the QRS complex, as projected upon the frontal plane.

\hat{A}_{QRS} is the QRS vector, and refers to both the magnitude and direction of QRS as projected upon the frontal plane.

The letter S , when placed before any of these symbols, makes the whole symbol refer to the true or absolute manifest area and/or direction of the vector in three-dimensional space, and not as it is projected upon the frontal plane.

All areas or magnitudes are expressed in units; each unit is one small rectangle of the electrocardiogram, or four microvolt-seconds.

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1. THE RELATIONSHIP BETWEEN THE VENTRICULAR GRADIENT, THE QRS COMPLEX, AND THE T WAVE OF THE ELECTROCARDIOGRAM

The relationship between these aspects or features of the electrocardiogram has been discussed by Wilson, Macleod, and Barker.² In the briefest possible manner we shall attempt to make this relationship clear by means of a concrete example. Let us take any human electrocardiogram and estimate the net QRS area and the net T area in Lead I and also in Lead III. Let us suppose that the net QRS area in Lead I is +5 units (20 microvolt-seconds), and that the net T (including any normal S-T segment shift) area in this lead is also +5 units. The + signs indicate that the larger deflection of the QRS and of the T is upright, or above the base line of the record. In Lead III, we may assume that measurement gives us precisely the same figures. In this case, then, the electrical axis, by Einthoven's triangle, of both the QRS complex and the T wave would be +60°. The gradient is obtained by taking the algebraic sum of the net areas of the QRS and T in each lead. These QRS-T sums are +10 in Lead I and +10 in Lead III. The direction of the gradient, as projected upon the frontal plane, is also +60° in this example, and its magnitude is obtained from the values in the two leads, as explained in the preceding paper. Here, its value is 20 units, or 80 microvolt-seconds.

Now we may accelerate this heart by administering amyl nitrite, and reduce the size of the T waves to half their former values. We shall assume that no change occurs in the size of the QRS complexes. The net QRS-T area in both leads, since the T waves are cut in half, is now +7.5 units. The direction of the gradient is still +60°, however. Although the gradient was reduced only 25 per cent, from 20 units to 15, the T-wave size is reduced by 50 per cent. With greater cardiac acceleration, the T waves may become low and diphasic, or isoelectric, and possess no net areas. The areas of QRS-T in both leads will now be +5 units, the gradient will lie at +60°, as before, and its size will be 10. Further cardiac acceleration may invert the T waves, so that the area in each of the two leads becomes -2.5 units. The algebraic sums, +5.0 and -2.5, are now +2.5 units in each of the two leads (in Lead II, of course, it would be +5.0 in this case); the gradient direction remains at +60°, and its size is 5 units. As a final step, let the gradient disappear. The T waves in all leads are now opposite the QRS complexes in average direction, and equal to the QRS complexes in area. Digitalis often has substantially this effect.

Of course, as was shown in the preceding paper, the directions of the QRS axis and of the gradient are not usually identical, even as projected on the frontal plane, and probably they are rarely identical in the normal heart, since normally an angle of about 30° separates the mean QRS axis ($S\hat{A}_{QRS}$) from the gradient ($S\hat{G}$), as these are located in three-dimensional space.

Local changes in the condition of the myocardium may change the direction of the gradient, and these may bring about abnormal changes in the T waves. For example, we may have net QRS areas like those in the example chosen, and the net area of the T wave in Lead I may also be +5 units. In Lead III, however, the net area of an inverted T wave may be -5, instead of +5 as in the first example. The figures from which gradient direction and size (G) are ascertained become +10 in Lead I, as before, but 0 in Lead III. The direction of the gradient is, therefore, $+30^\circ$, and its size is 11.5 units. A simple method of ascertaining magnitude is given in the preceding paper. The QRS axis still lies at $+60^\circ$.

Both the mean QRS axis (\hat{A}_{QRS}) and the gradient (G) are vectors, for they have magnitude and direction. Given the magnitude and

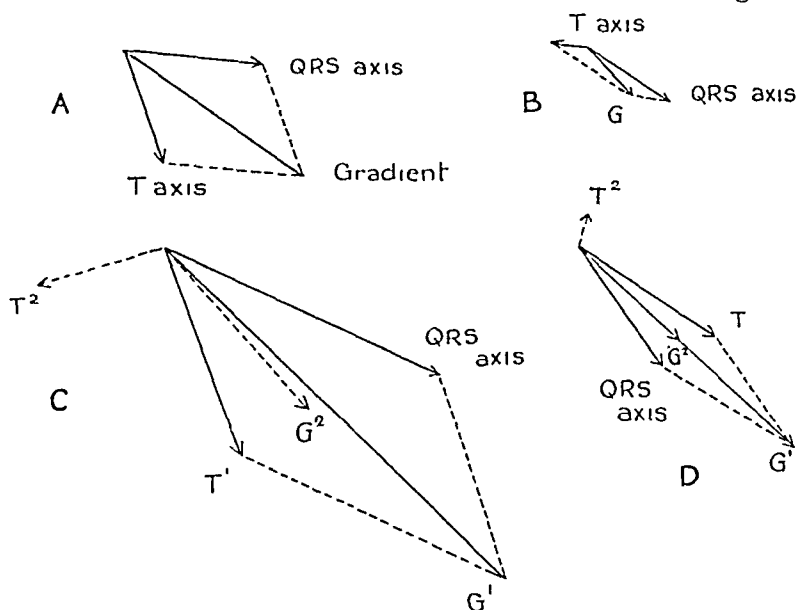


Fig. 1.—In A, the mean QRS axis (\hat{A}_{QRS}) is shown pointing to the left, forming an angle (angle α of Einthoven) of about 5° with the horizontal, or the line of Lead I. The heart is rotated in a counterclockwise direction around a longitudinal axis, which is not illustrated. Consequently the gradient, G , as explained in the preceding paper, points to the right of \hat{A}_{QRS} . Since the gradient, G , is the algebraic sum of the net areas of QRS and T, its manifest magnitude and direction, as projected on the frontal plane, as R. H. Bayley has shown, can be derived from the QRS and T vectors by a construction giving, as in elementary physics, the resultant of two forces. This parallelogram of forces can obviously also be employed to find any one of the three vectors if the other two are known. In this example, taken from a healthy, recumbent, medical student, the manifest area of QRS (\hat{A}_{QRS}) was 5 units, and, of G , 8 units.

Upon standing (B), because of rotation of the heart, mainly upon its long axis, \hat{A}_{QRS} shrank to 3.5 units and its direction became $+30^\circ$. At the same time, the direction of the gradient changed slightly, but it was reduced in manifest magnitude from 8.0 units to 2.3 units. As a consequence, as B of this figure shows, the T-wave axis now pointed to the right, and became inverted in Lead I. The electrocardiogram is shown in Fig. 4.

C shows the axes from a hypertensive patient. Her first record showed the axes labelled QRS, G^1 , and T^1 . Since they are drawn to scale, it can be seen that they are much larger than in the normal subject, although \hat{A}_{QRS} is still within possible normal limits, and G is not large. Three days later, with considerable acceleration of the heart rate, but while still recumbent, \hat{A}_{QRS} was unchanged, but the gradient, G , and the T axis have shifted to G^2 and T^2 , respectively. The T wave in Lead I is now sharply inverted. The electrocardiogram is shown in Fig. 5.

The T-wave changes in both cases are in reality caused by changes in the gradient. The axis of the T wave is forced to change when the gradient changes in magnitude, as the parallelograms show.

D simply represents a more usual picture with clockwise rotation. A decrease in G in such a case will bring about the typical decrease in the T waves which occurs upon changing from the supine to the standing posture, often with inversion of T_2 , and even of T_1 , as shown by G^2 and T^2 . Case 20, in Table III, and the electrocardiogram of Fig. 6 illustrate such an effect.

direction of \hat{A}_{QRS} and the mean T-wave axis, the direction and relative magnitude of the gradient, as projected upon the frontal plane, can easily be obtained by construction, as shown in Fig. 1. Or, conversely, given any two vectors, the other may be ascertained.

2. THE MATERIAL USED

The materials employed were the same as those used in the preceding study, except that, in the construction of the figures, data on sitting or standing subjects were excluded. Sixty additional electrocardiograms from patients without heart disease have been added, bringing the total to 270. All patients, even those without heart disease, were excluded if thyrotoxicosis or fever was present, for these affect the size of the gradient.

3. THE AVERAGE MAGNITUDE OF THE MANIFEST VENTRICULAR GRADIENT (G) AND MANIFEST MEAN QRS AXIS (\hat{A}_{QRS})

In normal persons, mainly below the age of 50 years, the average magnitude of G is about 13.0 units. The gradients of men are slightly larger than those of women. This is the explanation of the reported difference in the height of the T waves of men and women. However, when the sex difference in heart rate is allowed for, this difference in the size of the gradient becomes less, although it is still present. Tachycardia is much more common in women, and bradycardia in men. Of fifty subjects with heart rates of 60 or less in our series, nine were women. Of forty-one subjects with heart rates of 100 or more, only nine were men (Fig. 2.)

In contrast to the effect of heart rate on the size of the gradient, as discussed later, is its effect on the magnitude of \hat{A}_{QRS} . We are convinced, from a study of the rapid and slow hearts of the same subjects, that cardiac acceleration slightly reduces the net area of the QRS complexes. But this relation does not appear when the QRS areas of different persons are plotted against heart rate. This does not mean that there is no effect, but that it is masked by the other factors which cause far greater changes. There is, however, a sex difference in the size of QRS which is not dependent upon heart rate. In women this magnitude averages 5.9 units; and in men it averages 6.7 units. On the whole, therefore, at ordinary heart rates, G (13.0 units) is just about double A_{QRS} (6.3 units). Nearly 100 subjects were averaged in each group, so that the differences are statistically reliable within about ± 0.2 unit. In an earlier unpublished study, the QRS complex of women was found to be shorter than that of men, on the average. Since the units of QRS magnitude are time-potential units, a shorter duration, if the voltages are the same, would mean a smaller area, and, in this sense, the magnitude is related to the smaller average size of women's hearts. However, this is not necessarily the only reason for the difference.

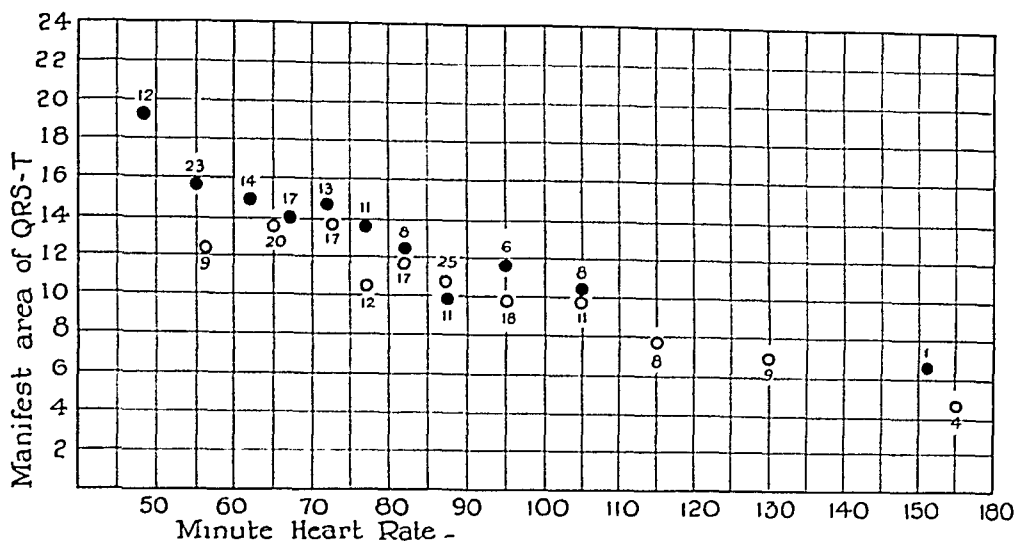


Fig. 2.—The relation between heart rate and the manifest area of QRS-T. Each figure indicates the number of subjects, the magnitudes of whose gradients were averaged to obtain the point on the graph.

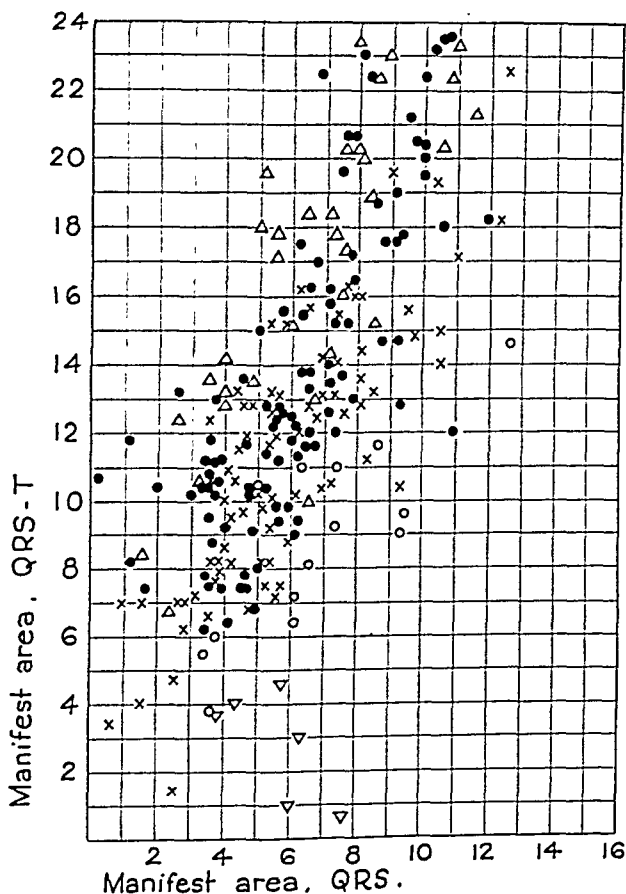


Fig. 3.—The relation between the manifest areas of QRS (A_{QRS}) and of QRS-T (G). Each point represents one subject. Deltas are from subjects whose heart rates ranged from 40 to 59/min.; solid circles, from 60 to 79/min.; X's, from 80 to 99/min.; open circles, 100 to 119/min., and inverted deltas, from 120 to 200/min. All subjects recumbent.

4. THE RELATIONSHIP OF HEART RATE, POSTURE, AND OTHER FACTORS
TO THE MAGNITUDE OF THE MANIFEST VENTRICULAR GRADIENT

(a) *A Comparison of Different Subjects.*—As the heart rate increases there is a progressive and apparently almost proportional fall in G. This is shown in Fig. 2. Since factors other than heart rate have a marked effect upon G, the range in G among different subjects at each heart rate is very great. For this reason, only the average manifest area (G) for men and women is shown in the figure. The numbers beside each point indicate the number of individual cases which were averaged to obtain the value shown. As nearly as can be judged from the data, there is practically a straight line relationship between heart rate and G. At every rate but one on the curve it will be observed that the average value of G for men is slightly higher than that for women. If the gradient size were plotted against the cycle lengths, a curve would be obtained, with its concavity upward, which might be fitted fairly closely to an exponential formula, but much larger numbers of cases would be required to demonstrate a valid relationship. Examination of all of the data, only part of which is given in Fig. 3, shows that most of the very slow hearts had large values for A_{QRS} . As will be shown in the next section, this is the reason why the point graphed for the twelve men in Fig. 2 appears to be out of line with the others. If a correction factor for A_{QRS} (manifest area of QRS) were applied in each case, in accordance with the relationship shown in Fig. 3, and the relationship between G and heart rate were then plotted, a smoother curve would probably be obtained. Observation indicates that the range in the size of the gradient at each heart rate would be somewhat reduced.

As explained in the first section, the effect of heart rate in reducing the size of the T wave is greater than its effect on the magnitude of the gradient (G).

(b) *Amyl Nitrite.*—Amyl nitrite was administered to six male medical students. The resulting increases in heart rate, decreases in size of gradient, and changes in the manifest mean area of the QRS (A_{QRS}) are shown in Table I.

TABLE I
EFFECT OF AMYL NITRITE

SUBJECT NO.	INCREASE IN HEART RATE, %	A_{QRS} BEFORE AMYL N., IN UNITS	A_{QRS} AFTER	% CHANGE	G BEFORE AMYL N., IN UNITS	G AFTER AMYL N., IN UNITS	% DECREASE
1	32	8.1	7.4	- 8.6	14.4	11.0	23
2	33	9.3	9.3	0	10.7	8.9	15
3	34	3.6	3.8	+ 6.0	9.5	6.4	33
4	54	3.5	4.2	+20.0	10.3	7.6	25
5	57	5.1	4.0	-22.0	8.4	2.9	65
6	64	6.5	5.9	- 9.2	16.0	6.3	61

It will be observed, from comparison of the second and last columns, that there is a very rough correlation between the percentage of decrease in the magnitude of the gradient and the percentage of increase in the heart rate. It must not be forgotten that G , as recorded, is the magnitude of \hat{G} , the projection of $S\hat{G}$ upon the frontal plane. As may be seen from inspection of the third figure of our first paper, under most, although not under all, circumstances, a movement of the heart which results in a change, either an increase or a decrease, in A_{QRS} will be associated with a change in the same sense, although not of the same degree, in G . In three of these subjects, changes, presumably in respiratory level, caused definite alterations in the direction of \hat{A}_{QRS} . These were subjects 3, 4, and 5. In the other three, changes of this kind were negligible. Associated with the change in direction of $S\hat{A}_{QRS}$ (see introduction) was a change in A_{QRS} , which is the magnitude as projected on the frontal plane. This effect was most marked in subjects 4 and 5. In subjects 1 and 6, the slight, although measurable, shrinkage or decay in A_{QRS} was, we believe, mainly an effect of the increased heart rate. In subject 4, particularly, the rate effect was more than offset by the change in direction of $S\hat{A}_{QRS}$. The change in direction, therefore, both increased A_{QRS} in this case and also opposed the shrinkage in G due to an increase in heart rate. Hence, the apparent decrease in the latter is much less than the absolute decrease, namely, the decrease in $S\hat{G}$. In case 5, A_{QRS} decreased because of a change in the position of the heart, and the same effect, acting on G , reduced it more than it would have been reduced by the rate change alone. Case 2 is slightly out of line, and the reason was that a slowing in heart rate from 120 to 100/min. occurred after amyl nitrite between the taking of Leads I and III; this slowing was greater than in the other cases.

We may estimate that, on the average, a 50 per cent increase in heart rate brings about a 39 per cent reduction in gradient magnitude. Fig. 2 shows that men whose average heart rate was 111 had gradients which averaged about 32 per cent smaller than men with heart rates of 74, i.e., 50 per cent lower rates, with the percentage based on the latter figure. The order of magnitude of the effects of induced and spontaneous rate change are, therefore, in fair agreement.

As stated in the preceding paper, amyl nitrite produced no measurable direct effect upon the directions of the vectors.

The effects on the gradient of a change in the position of the heart will be the subject of our third paper. Much additional evidence for the correctness of our interpretations will be found in that paper. If the examples cited above had been isolated instances of the phenomenon in question, we would not have discussed them.

(c) *The Valsalva Experiment.*—Observations were also made on seven subjects, using the Valsalva maneuver to accelerate the heart. The recumbent subject inhaled and then blew against the fluid in a water

manometer, maintaining the level at ten or fifteen inches H_2O pressure for twenty seconds. Because of the changing respiratory levels, the results are not as satisfactory as those obtained with amyl nitrite, but they show just as clearly the decrease in the magnitude of the gradient. In three subjects, the gradient reverted to normal size within three or four beats after the beginning of the reflex slowing of the heart which followed release of air from the lungs. In one subject, 50 years old, with marked reflex slowing, the gradient was reduced still further for the first beat or two at the low rate. In three subjects, a slight, but measurable increase in G appeared during the period of slower beating, and in one of these the slowing was very slight. With the beginning of the Valsalva experiment the changes are progressive, and apparently keep pace with the acceleration of the heart. Immediately after the release of air there are about five beats, often with further rate acceleration, before reflex slowing begins. These beats sometimes show an apparent gradient increase, and sometimes a decrease, but the results are doubtful because of the shift in respiratory level and the unknown effect on the electrical fields of excess air in the lungs.

(d) *Muscular Exercise*.—The effect of exercise upon A_{QRS} and G was studied in six subjects, two of whom were used twice, with different procedures. In four experiments the subjects were seated on a stationary bicycle, and the records were taken before, and at short intervals beginning immediately after, exercise. Unfortunately the ergometer was not in operation, so that a measure of the work done was not obtained, but it was relatively small. In four other experiments the subjects were recumbent when the records were taken, and the exercise, more severe in three cases, was standing running with simultaneous arm movements. To this group we have also added an excellent illustration from a recent paper by Twiss and Sokolow,³ and have studied the example published by Barker, Schrader, and Ranzoni,⁴ in which the exercise was more strenuous.

The results are given in Table II. In the seated subjects, who exercised relatively lightly, there was an apparent relation between the percentage increase in heart rate and percentage decrease in G . Since the changes in the QRS magnitude were negligibly small, no adjustment of the effects is necessary. In three recumbent subjects the manifest mean QRS area was reduced, and by about the same amount; in one it was increased; and in one there was no change, which is equivalent to a relative increase, for the dromotropic effect of the sympathetic should slightly reduce A_{QRS} . When the effect of exercise on the supine subjects is compared with the effect of amyl nitrite, it is evident that the decrease in G is relatively small in proportion to the increase in heart rate; and when correction is made for the decrease in A_{QRS} , the difference becomes even more striking. When Barker, Schrader, and Ranzoni's⁴ cases are examined, this fact becomes yet more evident. In their experiment, in spite of the severe exercise, and, in the unpub-

TABLE II
EFFECT OF EXERCISE

SUBJECT	% INCREASE IN HEART RATE	Δ QRS BEFORE EXERCISE	Δ QRS AFTER EXERCISE	% CHANGE	G SIZE BEFORE EXERCISE	G SIZE AFTER EXERCISE	% DECREASE
<i>Sitting</i>							
1	10	6.6	6.6	0	12.0	10.6	12
2	31	9.3	9.0	-3	14.2	10.7	25
3	31	5.9	5.8	-2	12.9	9.9	23
4	39	7.6	7.4	-3	12.4	7.3	41
<i>Recumbent</i>							
5	12	3.6	4.1	+14	9.5	8.2	13
2	28	11.6	9.9	-15	18.5	11.1	41
4	55	9.2	8.2	-11	16.2	11.2	31
6	56	7.2	7.2	0	15.4	13.4	13
T & S	83	5.1	4.4	-14	17.2	12.5	27

lished record, in spite of the great increase in heart rate, the T waves were actually increased in amplitude immediately after exercise, although, as the heart slowed, they became reduced. This increase in the height of the T wave does not mean an increase in G, because the waves were much narrower, but it is at least evident that the increased rate during severe exercise produces a far smaller reduction in G than the same rates during sinus tachycardia at rest or after amyl nitrite. In this respect, severe exercise is like fever or thyrotoxicosis.

In our experiments no increase in the height of the T wave was observed.

(e) *Change in Posture*.—In studying the effect of a change from the supine to the standing posture, we made use of four electrocardiograms published by Scherf and Weissberg⁵ (in their Fig. 5 we interchanged Leads III in *b* and *c*, on the assumption that they were reversed), and added 20 cases of our own. We found that the effects of standing, given in Table III, were precisely like those described by Scherf and Weissberg, and by others.

To increase muscular relaxation, our standing subjects leaned against a wall. Without exception, G was reduced in the standing, as compared with the supine, position. We are in complete accord with Scherf and Weissberg's⁵ statements that the change is not entirely dependent upon heart rate changes. The form of the QRS complex suggested very slight clockwise rotation on standing in about half the cases, and no appreciable change in most of the others. In two or three cases, however, very slight counterclockwise rotation around the heart's longitudinal axis of rotation was indicated. In most of the cases in which the mean QRS axis (\hat{A}_{QRS}) deviated to the right on standing, the gradient also deviated to the right, but the extent of the deviation of \hat{G} was less than that of \hat{A}_{QRS} . On the other hand, when \hat{A}_{QRS} deviated to the left, the leftward shift of \hat{G} was usually greater than the deviation of \hat{A}_{QRS} (Cases 3, 10, 14, 23). This means that, in

TABLE III

EFFECT OF CHANGE FROM SUPINE TO STANDING POSTURE

SUBJECT	BODY BUILD	% INCREASE IN HEART RATE	A _{QRS} SUPINE	A _{QRS} STANDING	% CHANGE	G SUPINE	G STANDING	% DECREASE	CHANGE IN QRS AXIS (F)	CHANGE IN QRS-T AXIS (F)
1	Hypersthenic	40	3.6	4.7	+31	9.5	6.7	30	+12°	+9°
2 (a)	Hypersthenic	22	5.5	5.0	-9	7.1	3.8	46	+22°	+12°
3	Hypersthenic	26	7.7	8.5	+9	12.1	9.5	21	-2°	-10°
4	Tall, hypersthenic	43	9.5	8.5	-11	21.0	13.8	34	0	-3°
5	Hypersthenic	7	5.6	7.9	+41	9.2	8.5	8	+9°	+14°
6	Short, sthenic	25	3.5	4.0	+14	10.3	7.4	28	+42°	+9°
7 (d)	Sthenic	34	5.0	3.5	-30	8.0	2.3	71	+26°	+8°
8	Short, sthenic	6	5.1	4.9	-4	11.0	9.0	18	-2°	-1°
9	Short, slender	31	6.5	5.1	-22	16.0	13.5	16	+14°	+12°
10	Short, sthenic	6	7.4	5.7	-23	14.0	10.4	26	-6°	-10°
11	Slender	43	7.6	7.5	-1	16.2	6.8	58	+27°	+11°
12 (b)	Tall, slender	11	18.3	21.0	+15	15.2	12.3	19	+7°	+7°
13	Tall, sthenic, muscular	15	4.8	5.0	+4	12.4	9.4	24	+19°	+4°
14 (e)	Slender	17	-2.3	-3.5	+52	7.6	3.4	55	-11°	-24°
15	Sthenic	34	6.7	6.2	-7	9.6	4.2	56	+10°	-8°
16	Heavy, sthenic	16	4.9	5.7	+16	10.5	6.8	35	+21°	-4°
17	Sthenic	17	1.6	0.8	-50	7.4	4.2	43	+23°	-4°
18	Slender to sthenic	14	10.8	9.3	-14	14.5	9.3	36	+3°	+2°
19 (d)	Sthenic	13	-4.9	-4.7	-4	7.0	5.1	27	+2°	-4°
20 (e)	From S & W, Fig. 1	41	10.9	11.0	+1	12.0	2.0	83	+3°	+5°
21	From S & W, Fig. 2	0	9.7	9.0	-8	14.8	10.0	32	+9°	+11°
22	From S & W, Fig. 4	20	5.3	6.2	+17	10.5	7.0	33	+7°	-13°
23	From S & W, Fig. 5	16	8.1	8.7	+7	8.7	4.2	52	-1°	-6°
24	From S & W, Fig. 5	31	8.1	8.4	+4	19.0	16.3	14	+3°	-11°

(a) The recumbent heart rate was 88, and this partly explains this subject's rather small gradient. Subject 5 had a supine rate of over 100.

(b) An example of the Wolff-Parkinson-White syndrome, which explains the large QRS areas.

(c) This subject's supine mean QRS axis was -96°, and changed to -107° on standing.

(d) More often than in patients, the normal subject's electrocardiogram was taken an hour or two after eating; this often reduces the gradient (Gardberg and Olsen⁹).

(e) Most of these subjects were medical students. Subject 20 was trained, and probably relaxed more on standing. In this case, G was difficult to measure accurately on standing because of its small net area.

(f) A plus sign means clockwise rotation around the A-P axis, that is, rotation to the right, and vice versa.

the majority of cases, \bar{G} shifted to the left *relative* to \hat{A}_{QRS} ; the average deviation was just 10° . Clockwise rotation of the heart on a longitudinal axis would produce this effect, but when \hat{A}_{QRS} deviated to the left on standing, \bar{G} should not have been deviated to the same extent if the effect is the result of rotation (section 5, preceding paper). We may conclude, therefore, that the increase in heart rate, as pointed out in our first paper, may be one factor associated with, or perhaps causing, the relative leftward deviation of \bar{G} . Clockwise rotation on the long axis is another factor. A third factor, associated with the standing posture itself, may possibly also have helped cause the relative leftward deviation of \bar{G} , but there is no direct evidence for the existence of such a factor.

The magnitude, A_{QRS} , increased about as often as it decreased, and sometimes the change was within the limits of error in measurement. There was no particular correlation between the changes in the magnitude, A_{QRS} , and the changes in direction of \hat{A}_{QRS} or in cardiac rotation. Nevertheless, in every case, the observed changes are readily explained by assuming that, on standing, most hearts become slightly more vertical in the sense that the base moves a little farther from the spinal column and/or by assuming a slight cardiac rotation (in two or three cases it was more than slight), either clockwise or counterclockwise on a long axis. When the electrocardiogram indicated that clockwise cardiac rotation had occurred, clockwise rotation proved to be required to explain the changes, and usually vice versa. Our third paper will deal more fully with this aspect of the question.

Mayerson and Davis⁷ have studied the effects of tilting table experiments upon the electrocardiogram. Their results were similar to ours and those of Scherf and Weissberg, although perhaps more exaggerated. In general, \hat{A}_{QRS} deviated to the right when the subject was raised from the supine to a nearly vertical position; the gradients, as in our experiments, deviated either to the right or to the left, and were reduced in size. The authors emphasized the T-wave changes, which amounted to inversion of T_2 and T_3 in some cases, and were accompanied by depressions of S- T_2 and S- T_3 exceeding 1 mm. in several instances.

For the benefit of those who wish to see for themselves whether the relation between the change in \hat{A}_{QRS} and \bar{G} (described under amyl nitrite) applies to the results in the table, it is pointed out that, in subject 14, \hat{A}_{QRS} shifted from -96° to -107° , and simultaneously increased in magnitude. Visualizing this in terms of the spatial axes, namely, $S\hat{A}_{QRS}$ and $S\bar{G}$ (Fig. 3 of the preceding paper), shows that, in this particular subject, \bar{G} should get smaller, not larger, with the increase in QRS area. The very large decrease in this subject's gradient, associated with only a moderate increase in heart rate, agrees with this conclusion. In subject 17, although the percentage change in \hat{A}_{QRS} was large, the absolute change was small. This must also be considered.

(f) *A Comparison of the Effects of Amyl Nitrite, Postural Change, and Exercise.*—Table IV shows the effects of amyl nitrite, postural change, and exercise upon the magnitude, G . In order to obtain a quantitative expression of the relative magnitude of the effects brought about by these factors, we have divided the average percentage decrease in G by the average percentage increase in heart rate. It will be seen that, in proportion to the increase in heart rate, postural change has a far greater effect than the other two procedures. Since there are twenty cases in this group and fifteen (with two subjects used twice) in the other two groups combined, the observed differences are undoubtedly significant. As explained above, our results also indicate that G is reduced more by amyl nitrite inhalation than by exercise, and this difference is the more striking when the supine, exercised subjects are considered. The difference did not appear in the seated, exercised subjects. After allowance is made for the changes in ΔQRS , the difference is still more obvious. Although the number of cases is small, our observations after exercise are, therefore, fully in accord with those of others, who have reported an actual increase in the height of the T waves during or immediately after exercise.

TABLE IV
A COMPARISON OF THE EFFECT OF AMYL NITRITE, EXERCISE, AND
STANDING POSTURE ON G

PROCEDURE	NUMBER OF EXPERIMENTS	I AVERAGE PERCENTAGE INCREASE IN HEART RATE	II AVERAGE PERCENTAGE DECREASE IN GRADIENT SIZE	II/I
Amyl nitrite	6	45.7	36.2	0.79
Exercise, sitting	4	27.8	25.2	0.91
Exercise, supine	5	46.8	23.0	0.49
All exercise	9	38.3	24.0	0.61
Standing posture	20	23.0	36.5	1.59

(g) *Ingestion of Food.*—It was pointed out by Gardberg and Olsen⁶ that the T wave became lower after meals in a majority, although not in all, normal subjects. The change began about an hour after eating and persisted for about two hours. The effect ranged from zero up to a 50 per cent reduction in T-wave height, which corresponds to approximately a 25 per cent decrease in gradient magnitude. The experiments were properly controlled and have been confirmed by us. We regard the possible effect of eating as the major uncontrolled variable in our present observations. Fortunately, the majority of the hospital electrocardiograms were taken in the forenoon.

4. THE RELATIONSHIP BETWEEN THE MANIFEST AREA OF QRS AND THE MANIFEST AREA OF QRS-T

According to the interpretation given in Fig. 3 of our previous paper, the net area of QRS in all limb leads may equal zero if, by chance, the

spatial QRS vector ($S\hat{A}_{QRS}$) points, or appears to point, straight backward at right angles to the frontal plane. We have encountered no electrocardiogram which gave a manifest QRS value of zero, but in several cases the areas were extremely small; in one the manifest area was only 0.2 units, and \hat{A}_{QRS} was apparently -60° . This was a hospital patient, 47 years old. He had a history which was compatible with, although not quite typical of, angina pectoris. He complained of dyspnea at night; his blood pressure was 124/84, and there were no signs of heart failure. His electrocardiogram was interpreted as being normal. His heart rate was 64/min. when the record was taken; G was 10.7, which is slightly small for the heart rate, but perfectly normal, as we shall see, in proportion to his A_{QRS} . The direction of \hat{G} was $+69.5^\circ$. If we are right concerning the position of $S\hat{A}_{QRS}$, it is obvious that his A_{QRS} could hardly have become smaller on standing. In fact, it increased to 2.7, and its direction became approximately -102° . The gradient, on the other hand, decreased to 2.1 units, and its direction (not very reliable in this case) shifted to $+44^\circ$. These changes are readily explained if we assume that, on standing, the cardiac apex tilted toward the left and backward *relative* to the base (or the base tilted to the right and forward) only a few degrees; and that, simultaneously, there was a very slight leftward shift of the gradient caused by the increase in heart rate from 64 to 75/min. or by the standing posture. Aside from the rather unusual character of the record, there was no electrocardiographic evidence of heart disease. The patient was not subjected to exercise.

We may now return to our main point. It should be clear from Fig. 3 of the first paper that when the area, A_{QRS} , is zero, the gradient, although foreshortened and relatively small, must still be of fair magnitude, as in the case just described. When the heart is in a more usual position, $S\hat{G}$, which now lies more nearly parallel to the frontal plane, should, on the average (due account being taken of posture and heart rate) be projected upon that plane as a larger G . G should achieve its maximum normal magnitude when the heart is in about the average position and rotated rather strongly in a clockwise fashion. In this position, also, A_{QRS} should approach its greatest normal magnitude. The facts, as far as they have been investigated, agree with these expectations, particularly with respect to the magnitude, A_{QRS} .⁸ Somewhat more vertical, although not extremely vertical, hearts are also likely to have large gradients, and this is also in line with expectation. The third paper, which will include roentgenographic and fluoroscopic evidence, will treat this phase of our subject.

Fig. 3 shows the relationship between A_{QRS} and G in supine subjects. The solid circles are from subjects whose heart rates ranged from 60 to 79, inclusive. The patient discussed above, although doubtfully normal, is added on the figure. Although the vertical scattering of points on the graph is rather great, as might be expected, there is, nevertheless, a fair degree of correlation between the magnitudes of

the vectors. No useful purpose could be served by treating this correlation statistically, for too many influences, aside from heart rate and A_{QRS} , may affect the gradient. Yet, when heart rate is stabilized in the recumbent subject, under basal conditions, these other factors probably have less influence than might be supposed. The rate range 80 to 99 is shown by the points marked x; the range 40 to 59, by deltas; the range 110 to 119, by open circles, and the range 160 to 200, by the inverted deltas. To avoid further confusion of points, the ranges from 100 to 109 and from 120 to 159 were omitted, although they showed the same correlation. In general, however, the faster the rate, the poorer the correlation between A_{QRS} and G . This means, we believe, that not all the sinus tachycardias selected were a consequence of the same causes, whatever those causes may have been. As A_{QRS} increases beyond about 8.0 units, there is a tendency for the largest gradient values to reach a ceiling, so that, with further increase of A_{QRS} , further gradient growth cannot occur. And, as our study of abnormal hearts shows, the gradient probably shows no increase when A_{QRS} is increased by hypertrophy or intraventricular block beyond the limits shown in the figure (see Case 12, Table III).

Even though the scattering of points is great in Fig. 3, it does suggest that, at each heart rate and A_{QRS} value, there is a minimum value below which G is not likely to fall in normal hearts; and a few of the points may possibly be abnormally high. For rates between 60 and 79, for example, there seems to be a definite sloping level below which the points rarely fall, and there are 101 points in that rate range. By extrapolation, we may infer that the gradient would nearly disappear at a heart rate of about 240/min.

The largest values of G were shown by thirteen hearts, all of whose G values lay in the range of 23.0 ± 0.6 units. This apparent ceiling is probably a coincidence. No doubt an occasional gradient will go higher. The upper limit of the normal value for A_{QRS} may be placed at about 11.0 or 12.0, although three hearts in 270 seemingly had larger values. None was above 12.6 units. The lowest presumably normal A_{QRS} value observed by us was in Case 14 (Table III), but there was a history of bronchial asthma. Nothing unusual was seen in the fluoroscopic examination, other than a very vertical heart. A_{QRS} was -3.5 units when the subject, a medical student, was standing. Since the present paper was first drafted, another similar record was obtained from a young physician concerning whose freedom from cardiac or pulmonary disease there is no doubt.

It must be emphasized that the gradient values are for recumbent subjects. The values of A_{QRS} will apply to seated subjects as well.

5. DISCUSSION OF INDIVIDUAL CASES

The most interesting example of a change in G was shown by a man, a normal medical student, who was the first subject discussed in the preceding paper because of the peculiarity of the directions of his axes.

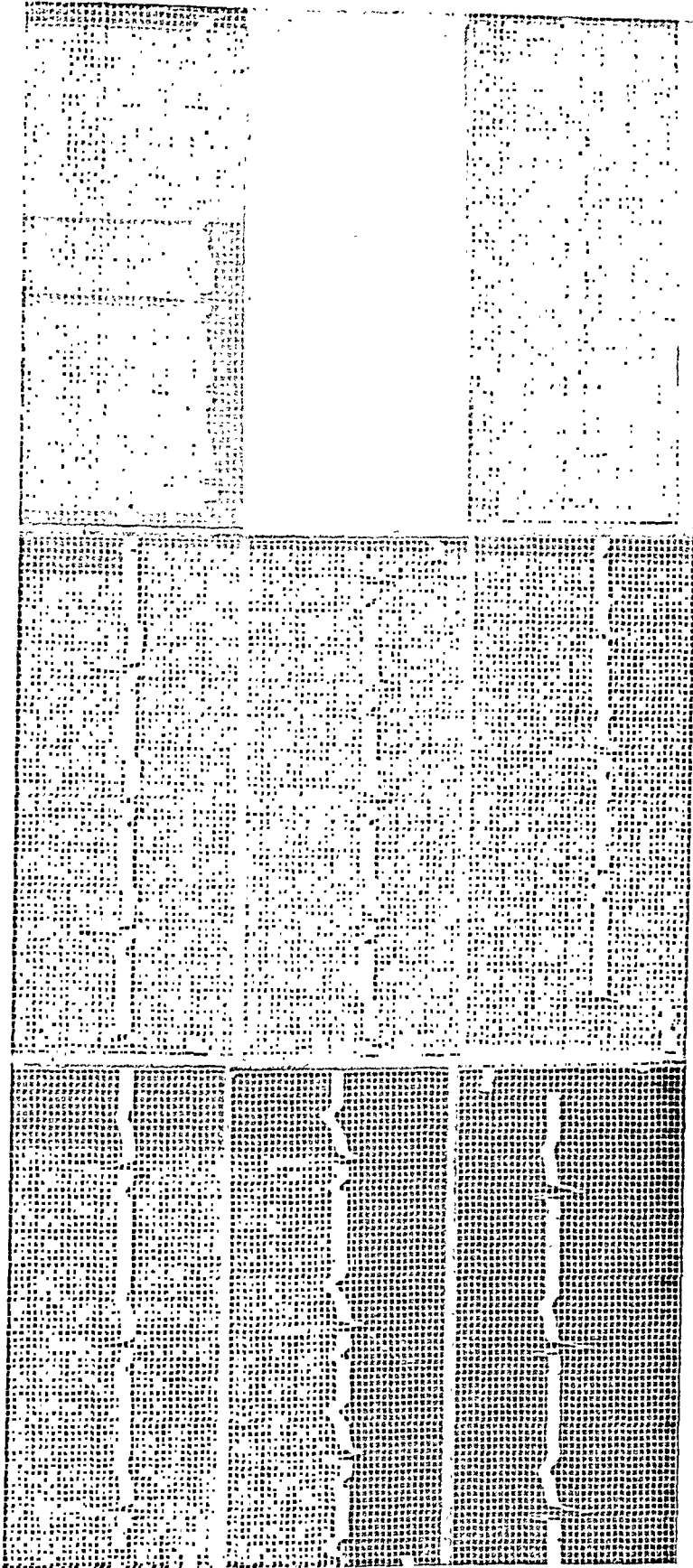


Fig. 4.—Electrocardiograms, before and after standing, from a healthy medical student, 23 years old. This is interpreted in the text and in Fig. 1; it is Case 7 in Table III.

When recumbent, his \hat{A}_{QRS} was $+4^\circ$, and its manifest area, 5.0 units. His gradient was at $+35^\circ$ and its manifest area was 8.0 units. Rather marked counterclockwise rotation of his heart was indicated by the form of his QRS complexes (Fig. 4). The degree of this cardiac rotation is unusual for a normal heart in a subject of sthenic habitus. Upon standing, \hat{A}_{QRS} was $+30^\circ$, and G was $+43^\circ$. At the same time, A_{QRS} decreased to 3.5 and G diminished to 2.3 units. A very moderate shift in the position of the heart would suffice to bring about all these changes, except the marked reduction in G . Evidently, there was cardiac rotation in a clockwise direction, that is, lessened counterclockwise rotation, and this is also shown by the character of the QRS changes. The position of the heart may have become slightly more vertical, as well. Both vectors, \hat{A}_{QRS} and G , were shortened. SG was shortened absolutely, as is typical upon standing. Fig. 4 shows the effect of these changes upon the T waves. T_1 becomes inverted. In this subject, because of the slightly unusual cardiac rotation, the characteristically normal diminution of the gradient could produce no other electrocardiographic effect. After amyl nitrite (Fig. 4), the net T area was again rendered negative in Lead I by depression of the S-T segment, although the T wave proper, so-called, remained upright. Quite incidentally, this observation should demonstrate that not all S-T segment shifts mean coronary disease or even temporary ischemia, for a vasodilator drug was employed. This point was brought out by Scherf and Weissberg.⁵ The changes in the form of the T waves which occur under these two conditions tend to show that the mechanism of the reduction in the size of the gradient brought about by the different procedures is not the same. Concerning this subject we can say, although not seriously, that standing produced digitalis-like changes, and amyl nitrite caused effects like those often ascribed to coronary insufficiency. It is evident that these differences deserve careful study, but investigation by the usual type of empirical observation may prove worse than useless.

Fig. 5A shows the electrocardiogram of a 32-year-old woman whose arterial blood pressure was estimated at 270/150. She also had a goiter, and had had no digitalis. The first electrocardiogram is fairly typical of long-standing hypertension and left ventricular hypertrophy. \hat{A}_{QRS} was 11.0 units in magnitude and its direction was $+23^\circ$. G was 17.2 units in magnitude, and its direction, $+42^\circ$. The axis of QRS-T lay to the right of the QRS axis, as is typical of a heart which is rotated counterclockwise (see preceding paper). The heart rate was 92/min. in Lead I. Three days later the electrocardiogram shown in Fig. 5G was taken. The heart rate was 119/min. in Lead I. The QRS axis was unchanged at $+23^\circ$, and the axis of QRS-T was $+48^\circ$. The change is slight, and the fact that the rate was slower in Lead III than in Lead I may be the cause. But the manifest area of QRS-T decreased from 17.2 to 9.2. On both occasions the patient was recumbent. As shown in the diagram of Fig. 1, the inversion of T_1 in the second record was

almost wholly the result of the reduction in G , which, in turn, may be almost fully accounted for by the increase in heart rate. Unfortunately, another record was not obtained, with reversion to a slower cardiac rate. We feel, however, that a classification of pictures of "left ventricular strain" into various types which depend upon changes in such a labile abstraction as the T wave may be a precarious undertaking. However, when the cardiac rate is within usual limits, changes in G , and, consequently, changes in the T wave, may prove to be of clinical significance.

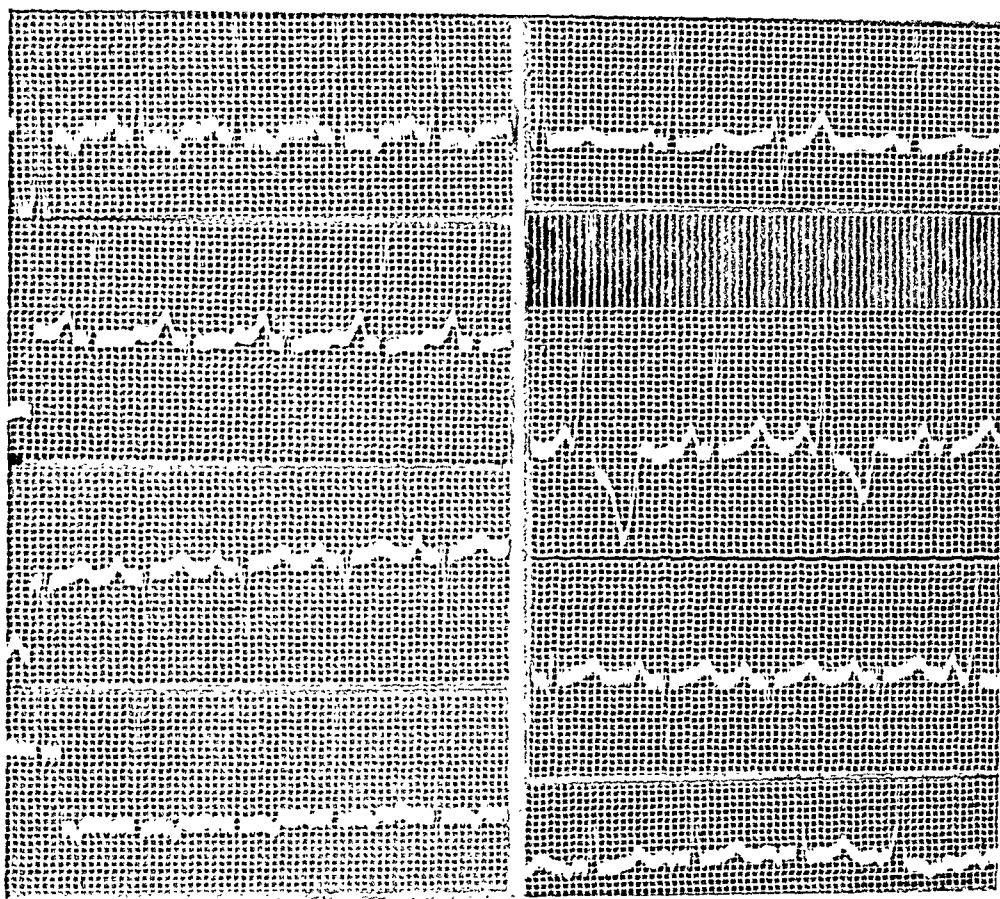


Fig. 5.—Electrocardiograms from a patient with hypertensive heart disease, before and after acceleration of the heart. Discussed in text and illustrated in Fig. 1.

6. DISCUSSION

The major problem which remains in electrocardiography is to discover the fundamental cause of the electrical forces which produce the ventricular gradient. The data presented in this paper and in the preceding one may assist us in solving the problem by indicating an appropriate type of animal experimentation. Even though this fundamental problem remains unsolved, it is, nevertheless, possible to attempt to explain the effect of one of the normal factors which reduces the magnitude of the gradient, namely, the effect of heart rate. It should be recalled that amyl nitrite, which is said to have little effect on the minute cardiac output,⁹ reduces the size of the gradient. Since the

heart is accelerated, the output per beat is reduced, and this may be a factor. During strenuous exercise, on the other hand, the output is increased to a greater extent than the rate,¹⁰ so that the output per beat is increased; yet the size of the gradient diminishes under the conditions of our experiments, but it may apparently be little reduced or even increased when the exertion is more severe.⁴ The standing posture slightly reduces cardiac output, at least in many persons, and, even in the absence of rate change, output per beat and gradient magnitude are reduced. In unpublished experiments, Mayerson and Davis,¹⁴ by means of the roentgenkymograph, observed a decrease in the size of the heart and a reduced stroke volume in their vertically placed subjects. A comparison of the several results indicates that at least two factors are concerned. One is the heart rate; the other may be the cardiac output per beat. Since all the procedures employed may be expected to bring about an augmentation of sympathetic tone, it is unlikely that this is an important factor in causing the *quantitatively* different effects, and Nordenfelt¹¹ has shown that the postural effects persist after administration of ergotamine tartrate.⁶ That reflex constriction of the coronaries plays a part is highly improbable, for, in order to cause a significant restriction of the oxygen supply to the heart muscle, an unphysiologic degree of constriction would be required. This is discussed by Scherf and Weissberg.⁵ Furthermore, it may safely be assumed that amyl nitrite causes coronary dilatation, yet the gradient is reduced. The only other important factor which is supposed to reduce the T waves, and, therefore, the size of the gradient, under the conditions of these experiments, is a change in the contact of the heart with tissues, the electrical conductivity of which differs.¹² It is unlikely that the effects of amyl nitrite can be ascribed to such a cause; and this may also be true of the changes which occur during the Valsalva experiment. Furthermore, the standing posture increases the QRS area about as often as it reduces it, yet the gradient is regularly reduced. It is reasonable to suppose that contacts between the heart and other thoracic structures should affect the magnitude of the one vector as much as they affect the other, but they are by no means equally modified. Alkalosis and acidosis⁴ may be ruled out by the promptness of the changes due to posture, a point emphasized by Mayerson and Davis.⁷

In the normally beating heart, therefore, there are two conditions which are associated with a change in the magnitude of the gradient. One is the heart rate; the other is the output of blood per beat, or the stroke volume. It should be noted that we do not say that stroke volume causes the gradient; we say that, under many conditions, a larger stroke volume is associated with a larger gradient, and vice versa. Other factors may, of course, modify the effects of these two, but their nature has not been demonstrated.

*Nordenfelt's conclusion was opposite to this; but, as a matter of fact, his figures show a reduction in gradient magnitude on standing, although this is relatively small. For this reason, depression of the S-T segments did not appear.

The effect of rate may be interpreted in the light of the following unpublished experiments. The ventricle of a turtle, at room temperature, was driven at various rates, and a record made of the monophasic action current at each rate. As cycle length shortened, the duration of the monophasic curve also shortened, along a curve similar to that which shows the relation between the Q-T interval and the heart rate.¹³ When the same ventricle was cooled about 10° C., its monophasic curve was nearly as short, when the cycle length was short, as was the monophasic curve of the uncooled ventricle at the *same* heart rate. But when the cycle lengths were long, the monophasic curve of the cooled muscle had nearly twice the duration of the curve from the uncooled muscle. The ventricular gradient most plausibly is a result of slower repolarization (i.e., longer monophasic curve) in some parts of the ventricles than in others. Hence, as in the turtle experiment, increasing the heart rate should cause a greater curtailment of the response in those regions which are normally slow to recover, like the cooled muscle, than in those regions which recover more promptly, like the uncooled muscle. When the durations of the excited state in the different regions become more nearly equal at higher heart rates, the electrical difference upon which the gradient depends is diminished, and, for this reason, the manifest area or magnitude of the gradient is reduced.

This interpretation satisfactorily accounts for the effect of heart rate on the gradient, although it does not prove that this is the real explanation. It throws no light whatever on the cause of those regional differences upon which the gradient depends. It is tempting to assume that the stroke volume is in some way related to the production of the normal gradient. More precisely, it may be imagined that the gradient depends upon the differential extent of shortening of subendocardial and subepicardial muscle fibers, and upon a correlated difference in energy expenditure and time required for electrical recovery. As stroke volume increases from zero, the gradient should increase, at first rapidly and then more slowly to a maximum, and should then slowly decline unless the decrease is offset by the rate effect. Most of the facts in our possession favor this interpretation, but so many uncertainties exist that an extended development of the hypothesis should not now be undertaken.

7. APPLICATION TO CLINICAL ELECTROCARDIOGRAPHY

In this and the preceding paper we have discussed factors which influence the normal direction and the magnitude of the manifest area of the QRS and of the ventricular gradient. We have given some evidence to show that the manifest area of the QRS is mainly dependent upon the direction, in relation to the frontal plane of the mean spatial QRS axis, $S\hat{A}_{QRS}$. However, it is also probably very slightly diminished during sinus tachycardia by a physiologic factor, namely, the accelerated velocity of conduction of the wave of excitation brought about

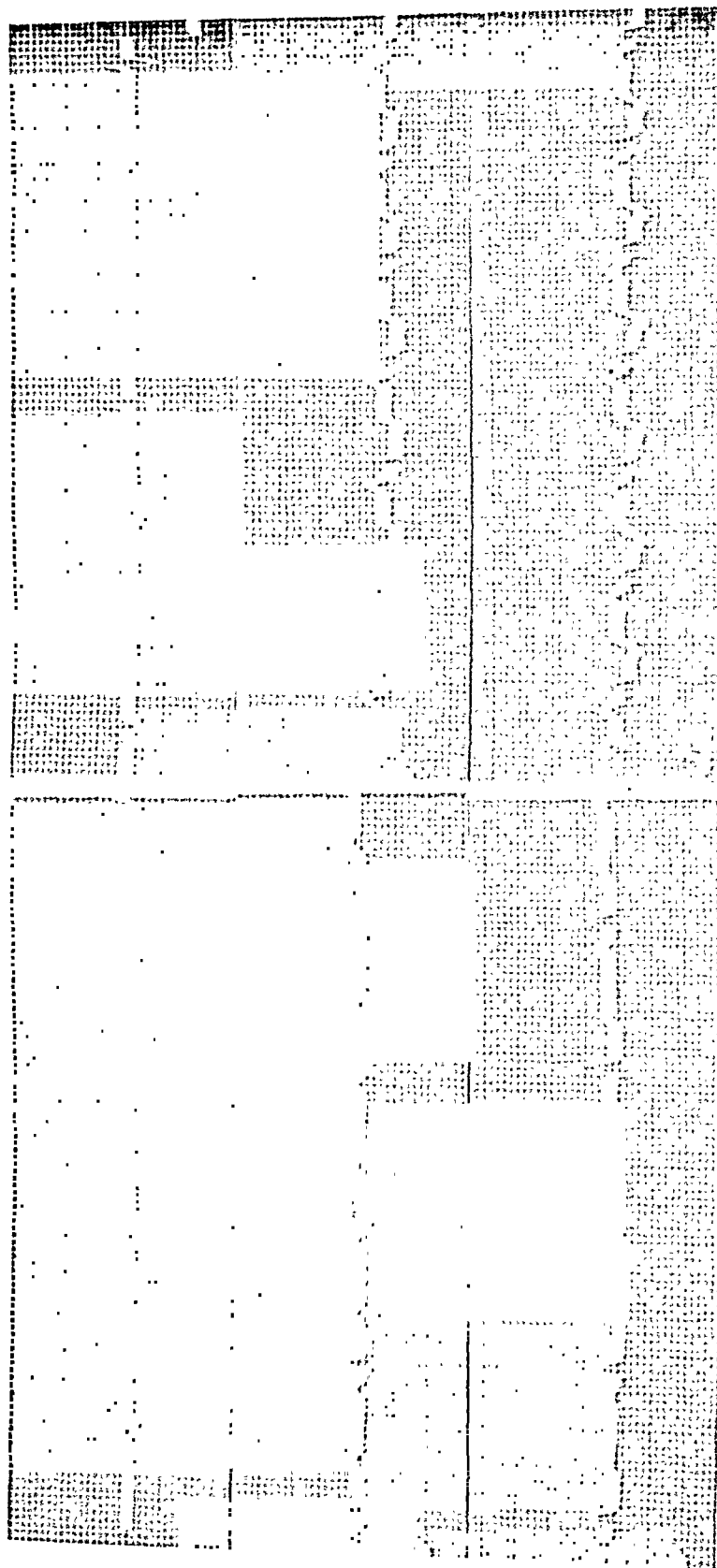


Fig. 6.—Electrocardiograms from a healthy student, aged 21, showing the effect of a change from supine to standing. This is Case 29 in Table III.

by augmented sympathetic tonus. The normal manifest area of the ventricular gradient, on the other hand, is affected not only by the direction of $\text{S}\hat{\text{G}}$, but by physiologic factors, the most important of which is heart rate. These apparently alter the magnitude of $\text{S}\hat{\text{G}}$. But the size of the gradient is also affected by another unknown factor which may be related to the stroke volume. Furthermore, the evidence thus far presented indicates that the absolute magnitudes of $\text{S}\hat{\text{A}}_{\text{QRS}}$ and $\text{S}\hat{\text{G}}$ in normal persons, under comparable conditions, differ much less than empirical observations could possibly have suggested. We believe that it is possible to make a fair estimate of the normal absolute magnitude of the vectors as they are projected in three dimensional space, and not merely on the frontal plane. This statement applies to the normal subject, for, as is well understood, abnormal changes may add to, or subtract from, that component of the vector which lies at right angles to the frontal plane without making their presence felt in the limb leads. Finally, as a rule, the three axes, namely, the longitudinal axis of rotation, H , the gradient, $\text{S}\hat{\text{G}}$, and $\text{S}\hat{\text{A}}_{\text{QRS}}$, normally lie very nearly in one plane and are separated by nearly constant angles.

If the foregoing statements are true, it then becomes possible to systematize three-lead electrocardiography so that it will not only be simpler to learn, but a more discriminating instrument for the detection of disease. Precordial leads, as hitherto, should detect those changes which produce electrical effects at right angles to the frontal plane, and what they reveal may assume new significance when correlated with the limb leads.

Our third paper will supply much additional evidence, and it will be given in a more quantitative fashion. Either in that paper, or in a subsequent one, we can consider the further question of the possible effect of thoracic shape and of structures of possibly different electrical conductivity upon the magnitude and direction of the axes. We do not deny that such effects exist, but it appears that they have relatively little effect upon the mutual relationships of the vectors.

SUMMARY AND CONCLUSIONS

Several of the factors which affect the manifest magnitudes of the mean QRS axis and of the ventricular gradient have been studied.

Both of these magnitudes are slightly smaller in women than in men, even when correction is made for the sex difference in heart rate.

Other things being equal, an increase in heart rate is associated with a decrease in the manifest magnitude of the gradient, and vice versa. The effect of increased rate is best demonstrated by a comparison of the effect of amyl nitrite and of exercise on recumbent subjects. Some subjects show a slight increase in the manifest magnitude of the gradient during the period of reflex cardiac slowing after the Valsalva experiment.

A change in posture from supine to standing invariably leads to a measurable decrease in the magnitude, G , and this change is too great to be caused by the cardiac acceleration. Often the decrease is extreme.

A comparison of the effects of the several procedures suggests that two separate factors are associated with the change in the manifest magnitude of the gradient, namely, heart rate and ventricular stroke volume.

On the average, in different subjects, the mean manifest areas of QRS and QRS-T show a direct correlation. This is interpreted in terms of a relatively fixed angle between the two axes, $S\hat{A}_{QRS}$ and $S\hat{G}$, and their projection upon the frontal plane of the body.

Two electrocardiograms are singled out for individual discussion. One, from a normal medical student, showed inversion of the T wave in Lead I when the subject was standing.

It is pointed out that the electrocardiographic approach which is being developed in these papers should not only make it possible to systematize the subject, but should also make electrocardiography a more discriminating instrument for the detection of disease.

One of the major implications of this study is that T-wave peculiarities or changes can be evaluated properly only when considered in relation to the magnitudes and directions of the mean QRS and QRS-T areas. This fact will remain true, even if it should be demonstrated that the actual magnitudes and directions of the vectors are not quite accurately given by the Einthoven triangle.

We wish to acknowledge, with thanks, the assistance given by Dr. J. L. Gouaux in making the fluoroscopic examinations, and by Dr. R. H. Bayley, who thoroughly criticized the manuscript.

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THE BENZOL-ADRENALIN TEST AS A RELIABLE METHOD
OF ESTIMATING CHANGES IN THE SENSITIVITY OF THE
DOG'S VENTRICLES TO FIBRILLATION. APPLICA-
TION OF THE METHOD TO THE STUDY OF
QUINIDINE SULFATE

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IN PREVIOUS papers,^{1, 2, 3} we reported the effect on the "fibrillation threshold" of the dog's ventricles of several drugs (procaine, digitalis, ouabain, papaverine, epinephrine, quinidine). The "fibrillation threshold" is the strength of the weakest short direct current stimulus which will induce ventricular fibrillation when applied directly on the ventricular surface in the last 0.04 to 0.06 second of ventricular systole, the so-called "vulnerable period." In those studies, ventricular fibrillation, once induced, was immediately stopped by the alternating current countershock method, and the fibrillation threshold, which was repeatedly ascertained, was shown to be constant, provided a few simple experimental precautions were taken. Therefore, this method allowed us to quantitate the effect on the fibrillation threshold of several physiologic,⁴ pharmacologic,^{1, 2, 3} and pathologic factors.⁵ This procedure is rather difficult and tedious in execution, and we therefore tested a simpler method of estimating the sensitivity of the mammalian ventricles to fibrillation.

It is well known⁶ that several drug combinations, such as chloroform-adrenalin, benzol-adrenalin, and cyclopropane-adrenalin, may induce ventricular fibrillation. Shen and Simon⁷ and Burstein and Marangoni⁸ made use of such drug combinations to study the action of procaine. They showed that procaine decreases the sensitivity of the mammalian ventricles to both chloroform-adrenalin⁷ and cyclopropane-adrenalin⁸ and prevents ventricular fibrillation. But, since ventricular fibrillation, once induced, leads to the death of the animal, their studies and similar ones consisted in comparing the reaction to chloroform-adrenalin, benzol-adrenalin, or cyclopropane-adrenalin of a control group of dogs with that of another group which received the protective drug. This statistical method of estimating the ability of a drug to prevent ventricular fibrillation is not entirely convincing, however, because, when a group of dogs are tested with chloroform-adrenalin, cyclopropane-adrenalin, and, to a lesser extent, benzol-adrenalin, some develop ventricular fibrillation, some show impressive runs of ventricular tachycardia, and others

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display only a few scattered ventricular extrasystoles.^{6, 9} On the other hand, any given dog, under constant experimental conditions, reacts constantly to the benzol-adrenalin combination. For this reason, repeated tests on the same dog before and after the administration of a drug are much more reliable as regards the efficacy of the drug under study.

In order to be conclusive, it is necessary to prove (1) that a dog's heart which develops ventricular fibrillation from benzol-adrenalin can be revived with an alternating current countershock; and (2) that such a heart, when repeatedly revived, will react repeatedly in the same way, and for a reasonable length of time, to benzol-adrenalin. These two requirements can be satisfactorily met, as is shown by the experiments reported in this paper.

METHOD

Dogs which weighed an average of 10 kilograms were anesthetized by the intravenous administration of 300 to 350 mg. per kilogram of sodium barbital. Under artificial respiration, the chest was opened through a midsternal incision and the heart suspended in a pericardial cradle. The mean arterial blood pressure was recorded on a kymograph from the femoral artery. An electrocardiographic tracing, generally Lead III, was recorded from subcutaneous electrodes. A standardized benzol-adrenalin test was performed as follows: Benzol was administered by intratracheal inhalation through an anesthesia bottle until the mean blood pressure fell 20 to 40 mm. Hg. Then, simultaneously, the administration of benzol was stopped and 0.02 mg. per kilogram (1:10,000 solution) of adrenalin was administered via the jugular vein. As soon as ventricular fibrillation was induced, two electrodes padded with cotton soaked in Locke's solution were applied around the ventricles, and short runs of a 60 cycle per second alternating current, 2 to 3 amperes in strength, were sent through the heart until the fibrillation stopped. A recovery period of at least fifteen minutes was allowed after fibrillation was stopped.

RESULTS

The results obtained in testing quinidine sulfate are illustrated by Fig. 1 and Fig. 2, which are pictures of the series of benzol-adrenalin tests performed in two typical experiments.

In the experiment of Fig. 1, the dog's mean blood pressure was 120 mm. Hg at 12:05 P.M. Benzol was then administered by tracheal inhalation. When the blood pressure had decreased to 70 mm. Hg, benzol was withdrawn and 0.02 mg. per kilogram of adrenalin was injected into the jugular vein. The blood pressure rose to 150 mm. Hg, and then ventricular fibrillation developed suddenly. The heart was immediately revived by the alternating current countershock method. At 12:45 P.M. a similar administration of benzol and adrenalin (0.02 mg. per kilogram) initiated ventricular fibrillation which was promptly stopped again with our reviving method. At 1:00 P.M. 15 mg. of quinidine sulfate (one per cent solution) per kilogram were administered via the femoral vein over a period of ten minutes. The blood pressure dropped from 110 mm. Hg to 50 mm. Hg. At 1:15 P.M. benzol-adrenalin (0.02 mg. per kilogram) did not produce fibrillation, although the blood pressure rose from

45 mm. Hg to 85 mm. Hg, but not as suddenly as in the control tests. Four more times the test was repeated. Arrhythmias, especially runs of ventricular tachycardia, developed, but ventricular fibrillation never occurred, despite the fact that in the last test, for example, the blood pressure rose from 65 mm. Hg to 115 mm. Hg, not very suddenly, however. At 3:05 P.M., i.e., almost two hours after the end of the quinidine

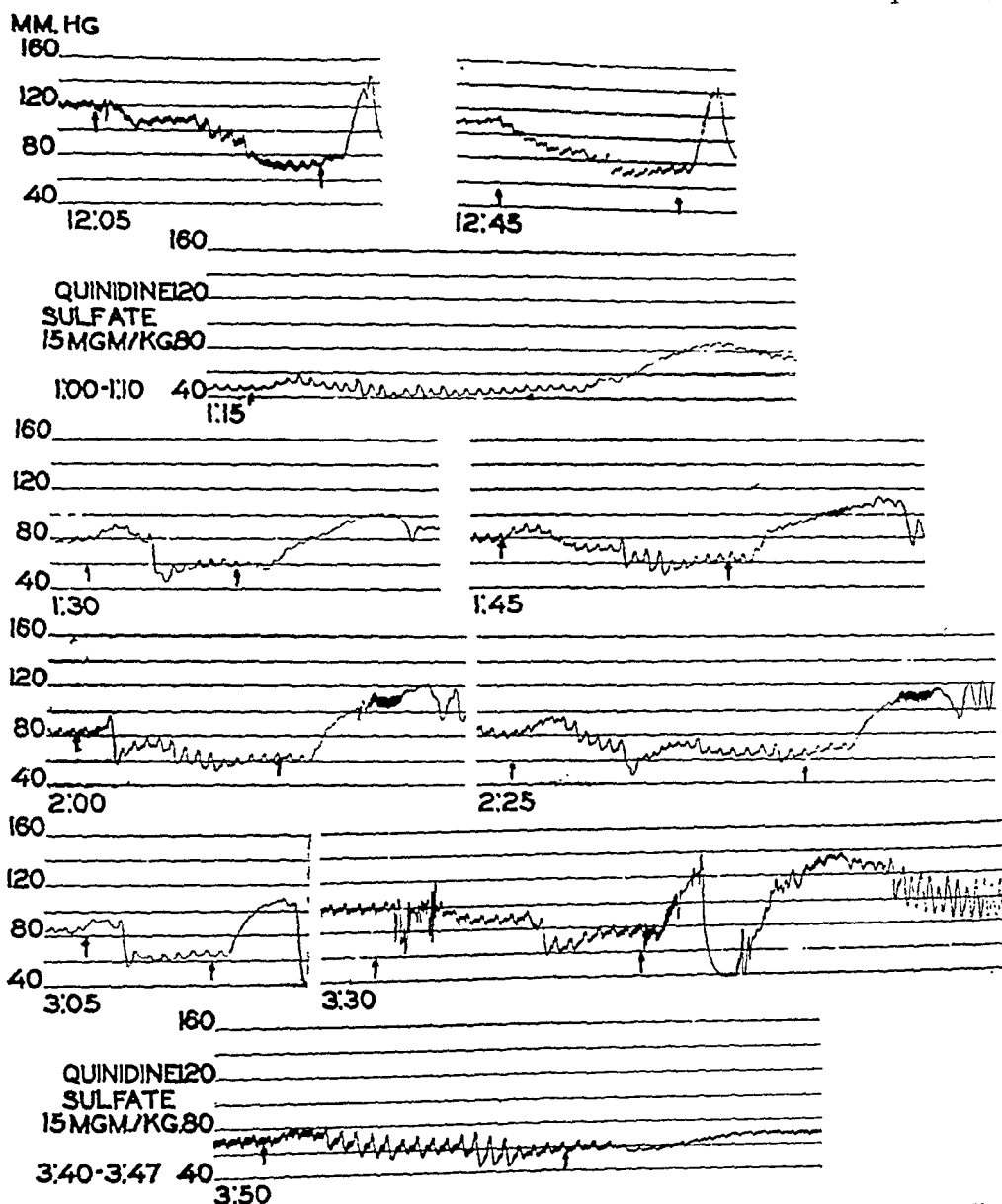


Fig. 1.—Tracing of the mean femoral blood pressure during each benzol-adrenalin test performed in a typical experiment during which rather large doses of quinidine sulfate were administered. Numerals on the left refer to mm. Hg and are the scale for the femoral blood pressure. Numerals below the tracing of each test refer to the time at which the test was performed.

administration, benzol-adrenalin (0.02 mg. per kilogram) induced ventricular fibrillation, although the blood pressure did not rise more (from 65 mm. Hg to 110 mm. Hg) or more suddenly than in the preceding tests in which fibrillation did not occur. At 3:30 P.M., benzol-adrenalin (0.02

mg. per kilogram) produced fibrillation again; the blood pressure rose from 80 mm. Hg to 140 mm. Hg. Fig. 1 shows the tracing of the mean arterial blood pressure before, during, and after revival from fibrillation by the alternating current countershock during this test. Between 3:40 and 3:47 P.M., another dose of 15 mg. per kilogram of quinidine sulfate was administered via the femoral vein, and, later on, benzol-adrenalin (0.02 mg. per kilogram) failed to induce ventricular fibrillation.

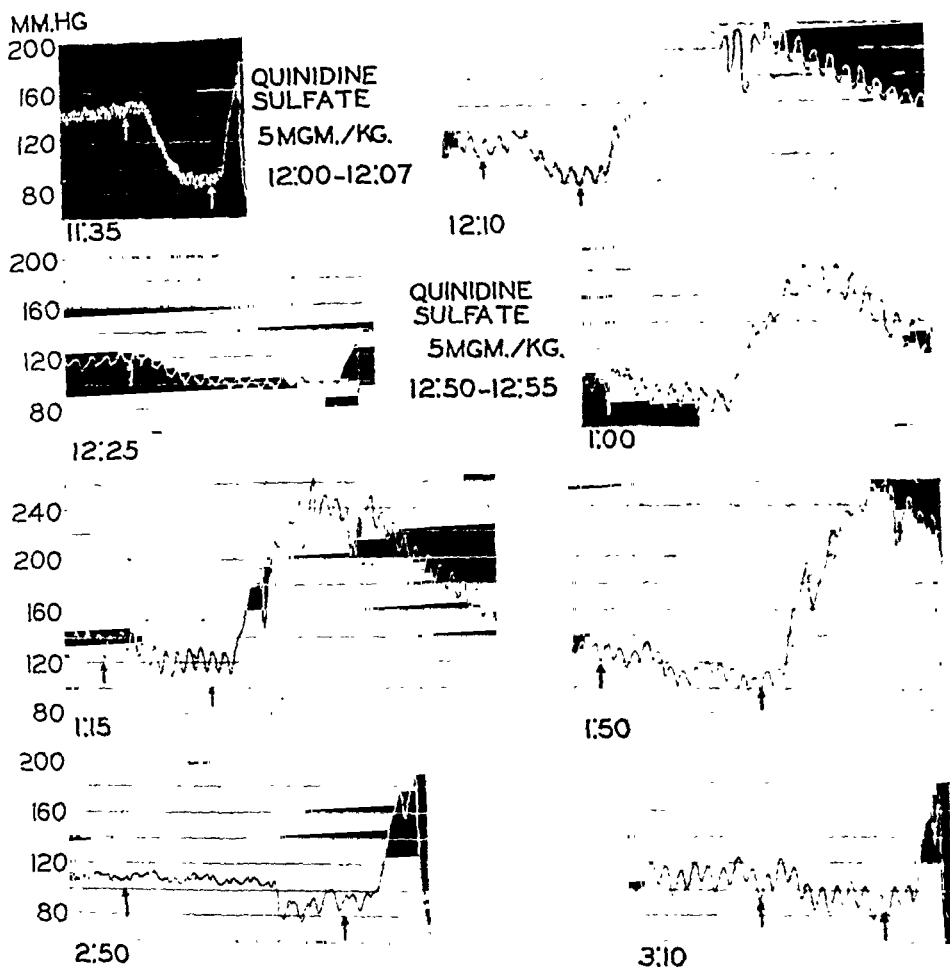


Fig. 2.—Tracing of the mean femoral blood pressure during each benzol-adrenalin test performed in a typical experiment during which smaller doses of quinidine sulfate were administered. Numerals on the left refer to mm. Hg and are the scale for the femoral blood pressure. Numerals below the tracing of each test refer to the time at which the test was performed.

This experiment evidently shows that quinidine sulfate prevented the fibrillation induced by benzol-adrenalin; yet, when the effect of quinidine was over, the heart still responded to benzol-adrenalin by developing fibrillation, which proves that the dog had remained under constant experimental conditions except for the administration of quinidine. A second administration of quinidine again prevented the benzol-adrenalin fibrillation.

The experiment of Fig. 2 is interesting in that small doses of quinidine sulfate, comparable to those used in the experiments reported by Wégria and Nickerson,³ were used.* At 11:35 A.M., after benzol inhalation, 0.02 mg. per kilogram of adrenalin increased the blood pressure from 90 mm. Hg to 180 mm. Hg and induced ventricular fibrillation, which was stopped by the alternating current countershock. From 12:00 to 12:07 P.M., 5 mg. per kilogram (1 per cent solution) of quinidine sulfate were administered via the femoral vein. The mean femoral blood pressure dropped from 120 to 100 mm. Hg. At 12:10 P.M., it was about 110 mm. Hg, and benzol-adrenalin (0.02 mg. per kilogram) did not produce ventricular fibrillation, although the blood pressure rose from 80 to 200 mm. Hg. At 12:25 P.M., benzol-adrenalin (0.02 mg. per kilogram) was administered; the blood pressure rose from 100 to 130 mm. Hg, and then fibrillation developed suddenly. After revival and recovery, an additional 5 mg. per kilogram of quinidine sulfate were administered. The arterial blood pressure temporarily dropped from 100 to 85 mm. Hg but soon stabilized around 95 mm. Hg and, at 1:00 P.M., benzol-adrenalin (0.02 mg. per kilogram) did not produce fibrillation, although the blood pressure rose from 70 to 185 mm. Hg. In two more similar benzol-adrenalin tests, at 1:15 and 1:50 P.M., fibrillation did not develop, and yet, in both tests, the blood pressure rose as suddenly and as high as or higher than in the control tests. At 2:50 and 3:10 P.M., respectively, two similar benzol-adrenalin tests induced fibrillation, but the blood pressure did not rise higher or more suddenly in these last two tests than in the preceding ones in which fibrillation did not develop.

This series of experiments shows that quinidine sulfate, in doses of about 15 mg. per kilogram, protects the dog's ventricles against the benzol-adrenalin fibrillation. With such doses of quinidine, the mean arterial blood pressure is significantly reduced for some time. In benzol-adrenalin experiments after the administration of such doses of quinidine, ventricular fibrillation does not develop, whether or not the blood pressure rises as much and as suddenly as in control tests. That protection lasts for some time.

Smaller doses of quinidine sulfate (5 mg. per kilogram) decrease the mean arterial blood pressure very slightly and only temporarily. During a benzol-adrenalin test after such doses of quinidine sulfate, the increase of blood pressure is the same or sometimes even greater than in a test before the administration of quinidine; nevertheless, such doses of quinidine protect the heart against benzol-adrenalin.

*In these experiments, the sinus node was clamped; the heart was driven at a constant and rather high rate by applying induction shocks to the right ventricle, and the fibrillating direct current stimulus was applied on the left ventricle. With such a preparation, we were never able to successfully use doses of quinidine sulfate greater than 2 mg. per kilogram, because larger doses depressed the myocardium and blood pressure too much and caused the heart to go progressively into failure. Apparently, hearts driven at a high rate by means of an artificial pacemaker cannot tolerate as much quinidine as do normally beating hearts.

SUMMARY

1. A new method of ascertaining repeatedly, in the same animal, the sensitivity of the dog's ventricles to fibrillation is presented.

2. This method is easier to perform than the "fibrillation threshold test," and yet it is critical. However, it does not quantitate the sensitivity to fibrillation. The procedure consists in comparing the reaction of the same dog to the combination of benzol-adrenalin before and after the intervention of some factor under study, such as a drug. This is done by ascertaining whether or not benzol-adrenalin, which induces fibrillation before the administration of the drug to be studied, still does so after the administration of the drug.

Whether or not the sensitivity of the heart to the benzol-adrenalin fibrillation could be quantitated by ascertaining the amount of adrenalin required to produce fibrillation remains to be studied.

3. Quinidine sulfate protects the dog's ventricles against benzol-adrenalin and prevents the benzol-adrenalin fibrillation, which confirms the results we obtained by the fibrillation threshold method.

4. The protection exists whether or not the dose of quinidine sulfate administered diminishes the increase of blood pressure which normally occurs during a control benzol-adrenalin test.

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THE INCIDENCE OF RHEUMATIC STIGMAS IN HEARTS WHICH ARE USUALLY CONSIDERED NONRHEUMATIC

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IN A previous study,¹ an attempt to find normal hearts which were free from rheumatic stigmas when examined microscopically according to the standard method of Gross, Antopol, and Sacks² was unsuccessful. Correlated with this fact is the observation at the autopsy table that one or more cardiac valves nearly always show some small degree of thickening in patients who had no clinical manifestations of endocarditis. The mitral valve is the one involved by far the most frequently (Fig. 1). Thickening is best observed along the line of closure. Often there is slight thickening, and, in some instances, there are adhesions among the chordae tendineae. The aortic valve may show slight adhesions along the commissures, and one or more leaflets of the tricuspid valve are often thickened and somewhat opaque in appearance. These considerations have induced us to investigate further the incidence of rheumatic stigmas in hearts which are usually considered to be free from rheumatic infection.

METHODS AND MATERIALS

A preliminary study was made of thirteen hearts which showed no valvular lesions save the minimal changes referred to above. Standard blocks were taken: one through each of the four valves, one from the posterior papillary muscle of the left ventricle, and the sixth block from the wall of the left auricle. The blocks were embedded in paraffin. Microscopic sections were stained with hematoxylin and eosin and with MacCallum's elastic tissue stain, and counterstained by van Gieson's method. Rheumatic stigmas were found quite abundantly in nine of these hearts, and somewhat sparsely in four of them. It was therefore decided to proceed with a larger number of cases. The preliminary study indicated that the block from the posterior papillary muscle was the most useful one for our purposes. Since it was necessary to depend for procurement of material largely on the cooperation of our residents in pathology, it was decided to ask routinely for blocks of the posterior papillary muscle (the anterior was used if it was larger than the posterior) and a block through the base of the left ventricle, including a portion of the posterior mitral leaflet and a small portion of the left auricle. It seemed to us more important to examine a large number of hearts in this way than a lesser number by the more complete method. We believe our data justify this decision. About 25 per cent of the material was obtained from autopsies performed by one of us (E. M. H.). Multiple blocks of the heart were obtained in many of these cases.

In all, 124 hearts were studied. Some of these, purposely included, contained recent or healed rheumatic valvular lesions or were the seat of bacterial endocarditis. This group of 12 hearts was used as a control series.

The larger group, consisting of 112 hearts, was free of gross, deforming valvular lesions, and in none of these cases had there been clinical evidence of rheumatic infection or chronic valvular disease.

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RHEUMATIC STIGMAS

The various stigmas were those commonly considered to be rheumatic. These were grouped under three headings, viz., vascular, perivascular, and interstitial. Essentially the same stigmas were used by Hall and Ichioka¹ in a previous investigation of calcific aortic stenosis. *Vascular lesions* included arteritis rheumatica, fibrinoid necrosis, and elastic tissue alterations. Under the heading of *perivascular lesions*, Aschoff nodules, fibrinoid swelling, and cellular infiltration were considered. The only *interstitial lesion* taken into account was cellular infiltration. Cellular myocardial scars caused by vascular changes of rheumatic origin were encountered in a number of instances. These are so difficult to separate from the scarring caused by arteriosclerosis of the coronaries that it was thought best not to include myocardial scarring. Edema is important in acute rheumatic lesions, but it is most likely to arise from other causes in the chronic forms.



Fig. 1.—Autopsy 22190. Ethiopian female, aged 30 years. Heart weight 310 Gm. Photograph of the heart showing a slightly nodular fibrous thickening of the leaflets of the mitral valve along their closing edges. Several of the chordae tendineae appear to be slightly thickened. The papillary muscles are hypertrophied.

Vascular and Perivascular Lesions.—Rheumatic lesions of the coronary arteries have been thoroughly studied by Karsner and Bayless.³ Von Glahn and Pappenheimer,⁴ in 1926, described in detail the peripheral vascular changes in acute rheumatic infections. These authors speak of swollen endothelium and swelling of the vessel wall, with reduction in the size of the lumen. In the acute phase, swelling is the result of infiltration of the walls with fibrin. Klinge⁵ refers to this as “fibrinoid Verquellung,” and the accompanying necrosis he calls “fibrinoid necrosis.” In acute rheumatic fever the infiltrating fibrin can be stained dark blue with Weigert’s fibrin stain, yellow with van Gieson’s stain,⁴ and pink with eosin (Fig. 2). In the chronic lesions of rheumatic heart disease, a fine, hyaline, fibrillary substance is found about the coronary arterioles in many instances. The wall of the arteriole may contain hyaline, finely granular patches (fibrinoid necrosis), or the wall may be thickened and completely hyalinized (Figs. 3 and 4).

Although the hyaline, fibrillary material about the vessel optically resembles fibrin, it no longer takes the fibrin stain. As von Glahn and Pappenheimer⁴ state, the fibrinous exudate is gradually changed into a permanent tissue (Fig. 5). This material now stains faintly red with van Gieson's stain and blue with Mallory's connective tissue stain. These perivascular scars are apparently healed phases of the fibrinoid reaction. Likewise, the hyalinized wall of the arteriole is also fibrous (Figs. 4 and 5).

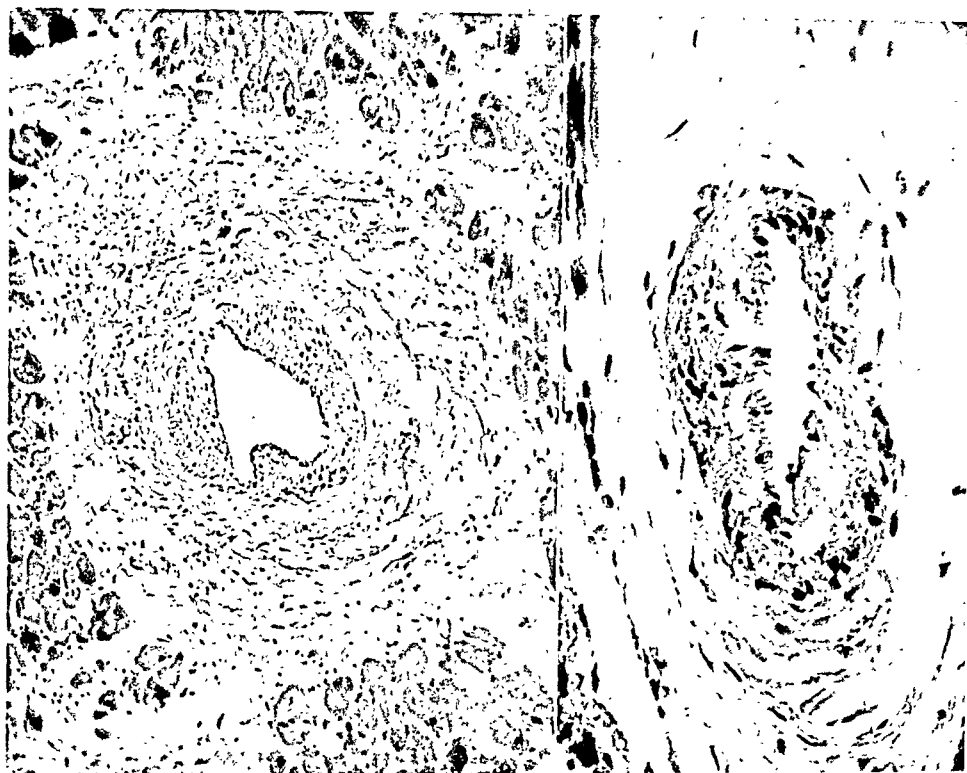


Fig. 2.

Fig. 3.

Fig. 2.—Autopsy S-4718. Caucasian male, 22 years of age. Heart weight 940 Gm. *Control case.* (Rheumatic heart disease and bacterial endocarditis.) This microphotograph of the heart illustrates fibrinoid necrosis and swelling of a coronary arteriole, also perivascular fibrinoid swelling as seen in a more acute phase. (H and E 100X.)

Fig. 3.—Autopsy 22305. Caucasian female, 61 years old. Heart weight 300 Gm. The microphotograph shows slight swelling and patchy fibrinoid necrosis of the wall, also some hypertrophy of the endothelium. (H and E 250X.)

Rheumatic arteritis has been used by us in a broad sense to include endothelial hyperplasia and hypertrophy, disarrangement of muscular elements (metallaxis), which is a characteristic and common feature in rheumatic infections, and infiltration of inflammatory cells within the vessel wall. The latter consist chiefly of large mononuclear cells (cardiac histiocytes), with a few lymphocytes, and occasional eosinophils. Since varying degrees of fibrinoid necrosis are usually present, there is a reduction in the number of smooth muscle nuclei, and those that remain often appear pyknotic (Figs. 6 and 7). Rheumatic arteritis is much more common in the acute rheumatic lesions than in the healed ones.



Fig. 4.

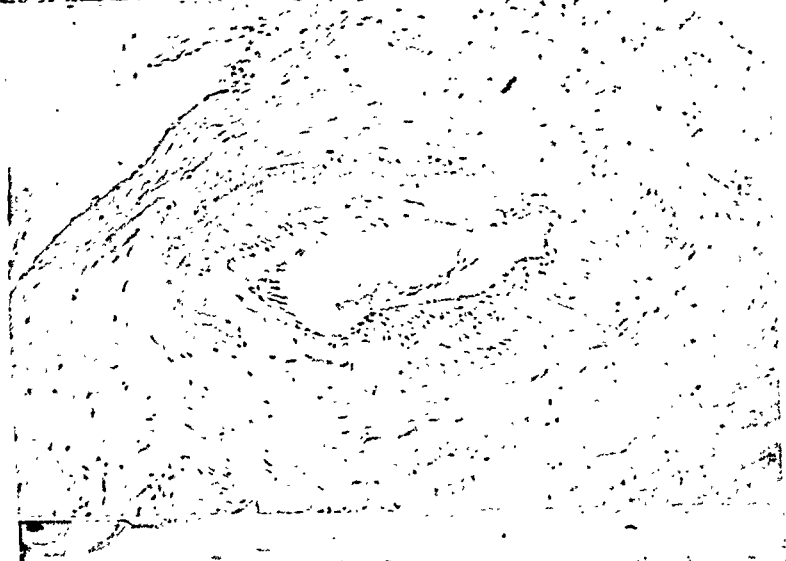


Fig. 5



Fig. 6.

Fig. 4.—Autopsy S-4409. Caucasian male, 63 years old. Heart weight 525 Gm. Microphotograph illustrating swelling or thickening of the vessel wall, with hyaline fibrous changes, probably the result of fibrinoid necrosis. The lumen is considerably narrowed. (H and E 130X.)

Fig. 5.—Autopsy 25731. Caucasian female, 86 years old. Heart weight 410 Gm. This microphotograph of a coronary vessel shows much the same thing as Fig. 4, a perivascular hyaline fibrillary mass which optically resembles what is, however, permanent fibrous tissue. (H and E 100X.)

Fig. 6.—Autopsy S-4388. Caucasian male, aged 29 years. Heart weight 225 Gm. (Acute glomerulonephritis.) Microphotograph of a coronary artery showing pale areas of patchy necrosis alternating with areas of increased cellularity (histiocytes). This is an example of arteritis. (H and E 250X.)

Fig. 7.

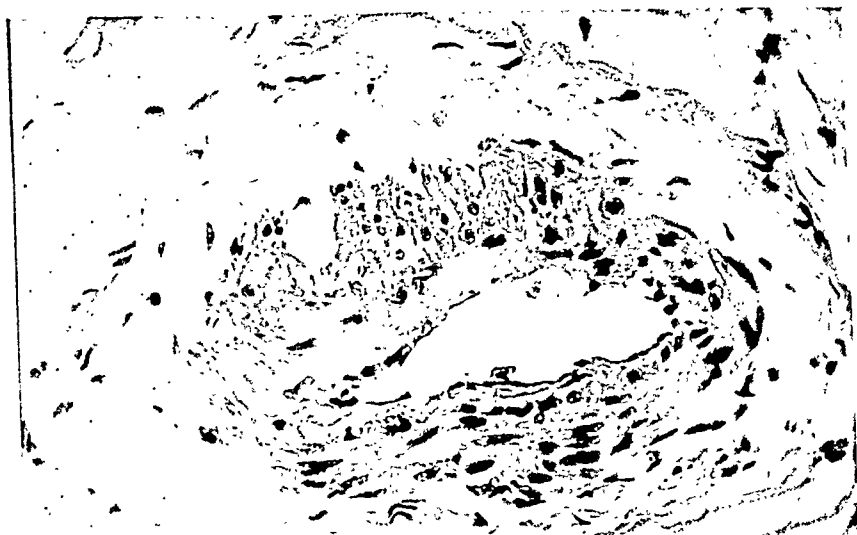


Fig. 8.

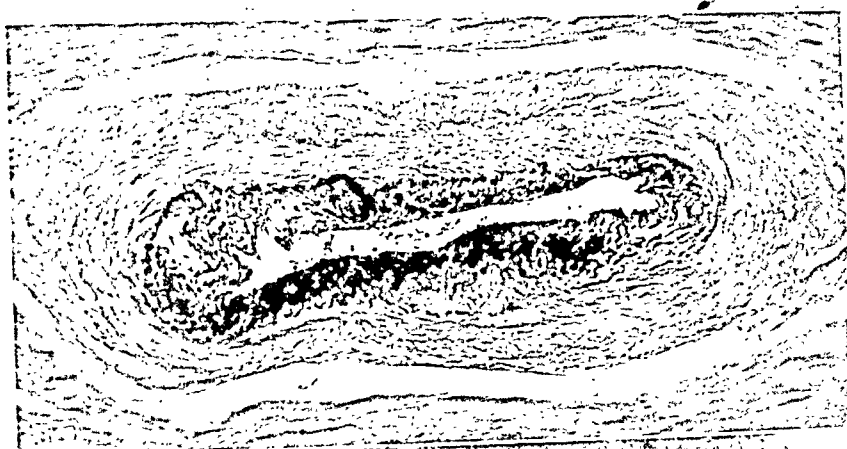


Fig. 9.



Fig. 7.—Autopsy S-4388. Same patient as in Fig. 6. Microphotograph illustrates same features as in Fig. 6, and, in addition, shows subendothelial edema, hypertrophy of endothelium, metallaxis, and perivascular fibrinoid swelling. (H and E 250X.)

Fig. 8.—Autopsy 25138. Caucasian male, aged 53 years. Heart weight 350 Gm. Microphotograph of a coronary artery showing alterations in the elastic tissue. The elastica appears greatly thickened, apparently because of splitting, fraying, and swelling of fibers. (MacCallum elastica stain and van Gieson stain.) (100X.)

Fig. 9.—Autopsy 25138. Same patient as in Fig. 8. Microphotograph showing a large collection of cardiac histiocytes or Aschoff cells. Aschoff body. (H and E 450X.)

As would be expected, therefore, only a few specimens revealed a marked degree of arteritis, but many presented minor changes of this character.

Elastic Tissue Alterations.—According to von Glahn and Pappenheimer,⁴ the elastic tissue changes are well marked in acute rheumatic infections. These authors describe swelling and beading of the elastica interna and alteration in the staining reaction. When exudation of fibrin is abundant, the lamellae may be difficult to distinguish and may disappear. Karsner and Bayless³ found elastica alterations in 90 per cent of their cases in the first two decades, and in all subsequent cases. They describe swelling, splitting, and fragmentation of elastic lamellae. Although many infections injure the elastica, these authors found that rheumatic fever produces early and serious damage to the elastica of the coronary arteries. Superficially, the elastica changes in our specimens appeared to be the result of hyperplasia. On closer study it was found that the process consists of swelling, splitting, fraying, and smudging (Fig. 8). Some degree of elastic tissue alteration was present in practically all of our hearts and was marked in nearly half of them.

Aschoff Bodies.—Most investigators accept the Aschoff body as a specific lesion of acute rheumatic heart disease. Aschoff bodies in chronic rheumatic lesions are not as characteristic as in the acute lesions.^{1, 6} In his monograph on rheumatism, Klinge⁵ describes and illustrates with a colored plate what he believes are the steps in the life cycle of the Aschoff nodule. After the typical granuloma stage, as seen in acute cardiac lesions, involutionary changes set in which cause the giant cells, fibrin, and hyaline matrix to disappear gradually; they are replaced by scar tissue which is more or less cellular. We agree with Klinge,⁵ Gross and Ehrlich,⁶ and others that the Aschoff body undergoes a series of changes as the rheumatic infection goes into a more chronic phase. Some Aschoff nodules lose their cellularity completely, and new ones appear with recurrent attacks of the disease. Masses of hyaline collagenous material are usually not present in the centers of Aschoff nodules during the chronic phase (Figs. 9 and 10).

Clawson⁷ has recently described the chief cell of the Aschoff body. This is a large, somewhat elongated mononuclear cell with a long, bar-like nucleus which gives off fine processes that extend through the cytoplasm toward the periphery. In cross section the nucleus is irregular in outline and appears to be suspended near the center of the cell by radiating lines of fibrillar material which pass outward to the cell membrane. According to Clawson,⁷ it is generally agreed that this cell develops from cardiac interstitial tissue and that it is restricted in its location to the myocardium and cardiac valves. He agrees with Downey that the cell should be called a cardiac histiocyte. Klinge⁵ uses the term "mesenchymal cells." These special histiocytes apparently increase in the myocardium under the stimulus of various irritants. Acute infections

caused by the pyogenic cocci call out polymorphonuclear neutrophils, as in other organs. Lymphocytes and plasma cells also appear in the myocardium in various chronic infections. Acute and subacute infections of the rheumatic type call out these particular histiocytes in considerable numbers. Occasionally the reaction is more exudative in type, causing an abundant fibrinoid reaction and a minimal proliferative response. Even so, nests of cardiac histiocytes (Aschoff bodies) may be found. It would seem, therefore, that cardiac histiocytes are not specific for rheumatic infections, but are specific as to the cardiac reaction to certain irritants. The response to the rheumatic virus is usually very active. They are likewise found abundantly in bacterial endocarditis, acute glomerulonephritis, and other streptococcal infections. The specimens in our series in which the other rheumatic stigmas were well represented were the ones in which Aschoff bodies were most frequently found.

Perivascular and interstitial nestlike collections of cardiac histiocytes we have called Aschoff nodules. If the cells are more loosely arranged and not so abundant we have referred to them as sub-Aschoff bodies or Aschoff-like nodules (Fig. 11).

Histiocytic Cellular Infiltration.—The perivascular and interstitial histiocytic response refers to an increase in the number of cardiac histiocytes in these areas. If the number of histiocytes was greatly increased, Aschoff nodules were almost invariably present. In a number of specimens in which histiocytes were abundant both about the vessels and in the interstitial spaces, multiple Aschoff nodules were found. In general, the histiocytic infiltration was the most variable among the stigmas considered.

Relation to Hyperergy.—A number of authors have expressed the view that the tissue changes in rheumatic fever are the result of hypersensitivity to some antigen, usually streptococci. Swift, Derrick, and Hitchcock,⁸ in 1928, expressed their views very clearly on this subject. Klinge⁵ has been the outstanding exponent in Europe of the view that rheumatic fever is related to hyperergy, and Rössle⁹ and Chiari¹⁰ are in agreement with him. Many names might be added to the list; in fact, it may be stated that the idea of hypersensitivity in relation to rheumatic infections is quite widely accepted. Although the etiology is not known, various types of streptococci have been so frequently associated with acute rheumatic manifestations that many investigators believe that they are etiologically important, if not the actual cause of the disease.

By repeated parenteral injections of horse serum in rabbits, Klinge¹¹ was able to produce a hyperergic arthritis, accompanied by Aschoff-like granulomatous lesions about the small coronary arteries. Vaubel,¹² employing the same experimental procedure, likewise obtained hyperergic carditis. Small quantities of horse serum, injected subcutaneously at intervals of several weeks, provoked a mild response, and larger amounts, by the intravenous route, resulted in a severe hyperergic

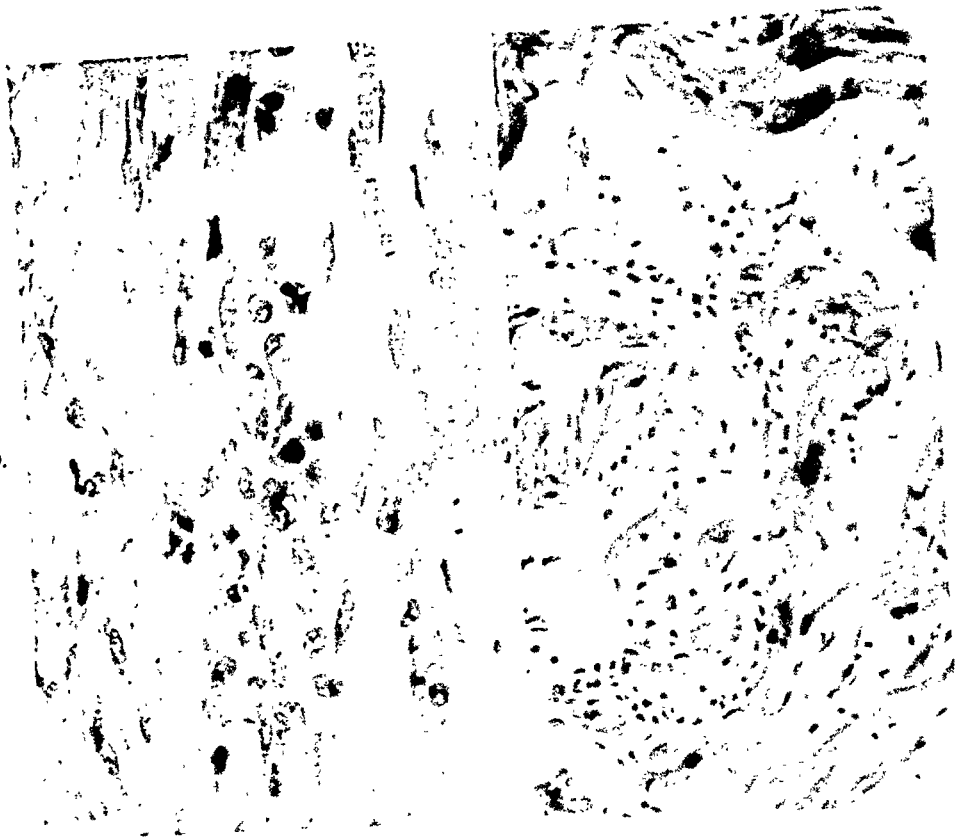


Fig. 10.—Autopsy 26208. Caucasian male, 60 years old. Heart weight 650 Gm. Microphotograph showing collection of cardiac histiocytes to form an Aschoff body. (H and E 400X.)

Fig. 11.—Autopsy 22265. Caucasian female, 61 years of age. Heart weight 360 Gm. Microphotograph illustrating a loose collection of perivascular cells, mainly histiocytes. Such collections the authors have called Aschoff-like or sub-Aschoff bodies. (H and E 200X.)

Fig. 12.—Experimental lesion in a coronary artery of a rabbit produced by multiple injections of horse serum intravenously in large doses (2-20 c.c.) over a period of 6 to 7 weeks. The microphotograph shows endothelial hyperplasia, edema of the subendothelial layer, and marked increase in histiocytes throughout the muscularis. There is some perivascular increase in mononuclear cells, also infiltration of the endocardium with similar cells. (H and E 100X.)

TABLE I
CONTROL CASES (KNOWN RHEUMATIC OR BACTERIAL ENDOCARDITIS)

CARDIAC VALVES THICKENING												VASCULAR				PERIVASCULAR				PRINCIPAL LESIONS
NO.	AGE AND SEX	HT. WT.	HIS- TORY RHEUM. FEVER	FUSION COM- MIS- SURES	AORTIC	MI- TRAL	TRI- CUSP.	ARTE- RITIS	FIBRI- NOID NE- CRO- SIS	ELASTIC TISSUE HYPER- PLASIA	ASCHOFF BODY	FIBRI- NOID SWELL- ING	CELLU- LAR INFIL- TRA- TION	INC. MESEN. CELLS	PERI- CAR- DIUM					
1	M 8	345	+	-	-	-	-	++	++	++	+	+++	+++	+++	+	Rheu. pericard. (subac.) Myocarditis (acute)				
2	F 9	300	+	-	-	+	-	++	++	+++	+	+++	+++	++	+	Rheu. pancarditis. Subac. pericarditis.				
3	Mex. M 12	250	+	-	-	ch. veg.	-	++	++	+++	+	+++	++	+++	+	Ac. bact. endocard. Osteomyelitis. Abscesses myocardium.				
4	M 22	940	10 yr. +	-	rolled +	veg. +	-	++	+++	+++	+	++	+++	+++		Subac. bact. endocard.				
5	M 37	440	N.R.	-	-	veg. + rolled	-	+++	+++	+++	+	+++	+++	+++		Ac. rheu. heart disease.				
6	M 37	500	+	-	+	++	+	++	++	+++	-	+++	+	+		Rheu. heart disease. Mitral stenosis.				
7	M 39	960	N.R.	-	veg. ++ rolled	veg. ++ nod.	-	+	+	++	±	++	++	++		Chr. rheum. endocard. Subac. bact. endo. Syph. aortitis v. insuff.				
8	M 54	745	±	+	++	+	-	+	+++	++	-	+++	+	+		Chr. rheu. endocard.				
9	F 54	550	Chorea	-	veg. +	+	-	+++	++	++	+	+++	+++	++	+	Ac. bact. endocard. Ac. fibrinous pericard. Rupture of heart.				
10	Col. F 58	480	+	+	-	++	-	++	++	+++	+	+++	+	++		Rheu. heart dis. Mitral stenosis.				
11	M 65	660	N.R.	-	-	veg.	-	++	+++	+++	+	+++	++	+++		Bact. endocard. (Str. viridans)				
12	M 75	500	+	-	veg. +	-	-	++	++	++	+	+++	+++	++		Adenoca. sig. colon. Chr. rheum. endocard. Bact. endocard.				

carditis with profound involvement of the coronary arteries. Hemken,¹³ working in our laboratory, produced similar results in rabbits by 9 to 10 intravenous injections of horse serum over a period of 6 to 7 weeks. Mild lesions were produced by small doses of 0.5 c.c. to 2.0 c.c. Profound changes were obtained with larger doses, ranging from 2 to 10 c.c. These changes closely parallel those of rheumatic arteritis in man; in fact, all of the stigmas described above are duplicated, including even granulomatous nests of histiocytes. An excellent example of experimental hyperergic arteritis is presented in Fig. 12.

RESULTS

Controls.—As stated previously, 12 cases of proved rheumatic and/or bacterial endocarditis were used as controls (Table I). The ages ranged from 8 to 75 years. There were 9 males and 3 females. A history of rheumatic fever was obtained in 8 cases, and of chorea in 1 case; there was no record in 3 cases. The smallest heart (250 Gm.) was from a Mexican boy, 12 years of age. All of the hearts were enlarged; the two largest weighed over 900 Gm. Mycotic vegetations were present on the mitral valve leaflets in only 6 cases and on both mitral and aortic in 1 case. In four of the remaining cases there were only healed rheumatic lesions. No valvular lesions were evident in a boy of 8 years, although subacute rheumatic pericarditis and myocarditis were present. In two cases of subacute bacterial endocarditis no previous rheumatic lesions were demonstrated.

The various stigmas of rheumatic infection were well represented in all but one case, as shown in Table I. In this case (No. 7), a man of 39 years, there was a combination of chronic rheumatic valvular disease and mycotic vegetations affecting both mitral and aortic valves, together with syphilitic aortitis and aortic insufficiency. Aschoff nodules were present in 9 cases (75 per cent), a sub-Aschoff nodule in one, and in two cases no specific granulomas were found.

Main Group of 112 So-Called Nonrheumatic Hearts.—A history of rheumatic fever was recorded in only 3 cases, a negative history was found in 16, and no record was obtained in 88. Frequent sore throats were recorded in 2 instances, and there was a history of scarlet fever in 5.

Incidence of Minimal Valve Thickening.—The minimal lesions, in the form of thickening of valve leaflets, fusion of commissures of the aortic valve, and thickening of chordae tendineae are presented in Table II.

TABLE II
SUMMARY OF GROSS CHANGES IN CARDIAC VALVES

	FUSION OF COMMISSURES	THICKENING OF LEAFLETS			THICKENING OF CHORDAE	
		AORTIC	MITRAL	TRICUSPID	MITRAL	TRICUSPID
No. cases (+)	14	10	65	22	42	9
No. cases (++)	0	3	9	0		
Total	14 (12.5%)	13 (11.6%)	74 (66.0%)	22 (19.6%)	42 (37.5%)	9 (8.0%)

TABLE III
SUMMARY OF RHEUMATIC STIGMAS IN 112 HEARTS

	VASCULAR						PERIVASCULAR						INTERSTITIAL	
	ARTERITIS RHEUM.		FIBRINOID NECROSIS		ELASTIC T. ALTERATION		ASCHOFF BODIES		FIBRINOID SWELLING		CELLULAR INFILTRATION (HISTIOCYTIC)		CELLULAR INFILTRATION (HISTIOCYTIC)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Slight (+)	31	27.7	12	10.7	7	6.16	*34	30.3	10	9.0	46	41.0	47	42.0
Mod. (++)	69	61.6	24	21.4	52	46.4	33	29.5	65	58.0	51	45.5	52	46.4
Marked (+++)	9	8.03	76	67.8	53	47.3	0		37	33.0	13	11.6	9	8.03
Absent (-)	3	2.70	0		0		45	40.18	0		2	1.87	4	3.5
Total	112		112		112		112		112		112		112	

*Sub-Aschoff bodies.

In 14 instances (12.5 per cent) the aortic commissures were fused to a slight degree (+). The aortic cusps were slightly (+) thickened in 13 cases (11.6 per cent). The mitral leaflets were the seat of minor thickening in 74 cases (66.0 per cent). The chordae tendineae of the mitral valve were thickened in some degree in 42 instances (38.4 per cent). The tricuspid leaflets were slightly (+) thickened in 22 cases (19.6 per cent). All of these percentages are probably low because most of the hearts were described by residents in pathology who in many instances failed to record minimal changes in the valves. In spite of this fact the mitral valve was thickened in 66 per cent of the specimens.

Incidence of Microscopic Rheumatic Stigmas.—These are presented in Table III. The arteritis was mainly slight to moderate. Fibrinoid necrosis, fibrinoid perivascular scarring, and elastic tissue alterations were principally in the moderate (++) and marked (+++) columns. Aschoff bodies were found in 33 instances, or 29.5 per cent, of the cases, and sub-Aschoff nodules in practically the same number, i.e., 34 times, or 30.3 per cent. In forty-five cases there were no cell nests that could be classified as Aschoff bodies.

Increase in perivascular and interstitial histiocytes was chiefly slight to moderate. There was a marked increase in roughly 10 per cent of the specimens.

TABLE IV

INCIDENCE OF MINIMAL, HEALED RHEUMATIC INFECTION IN 112 HEARTS, SHOWING ALSO DISTRIBUTION ACCORDING TO DECADES

NO. OF CASES	AGES (DECADES)	RHEUMATIC INFECTION		
		POSITIVE	PROBABLE	DOUBTFUL
3	0-10	2	1	0
3	11-20	1	2	0
6	21-30	2	3	1
9	31-40	5	3	1
18	41-50	13	4	1
22	51-60	14	7	1
29	61-70	16	11	2
17	71-80	10	5	2
5	81-90	5	0	0
Total 112		68 (61.7%)	36 (32.1%)	8 (7.2%)

The distribution of cases by ages (decades) and the number of those classified as positive, probable, or doubtful as regards rheumatic infection are recorded in Table IV. Comparatively few cases (21) fell in the first four decades. This is because the majority of patients in the Los Angeles County Hospital are in the older groups. Of five cases in the ninth decade, all were considered positive for rheumatic infection, i.e., healed lesions were present which could be classified according to the stigmas observed as resulting from contact with the rheumatic virus.

Of the so-called positive cases there were 68 (60.7 per cent) in all; 36 (32.1 per cent) were in the probable rheumatic group, and only 8 in the doubtful column.

TABLE V
SAMPLE OF LARGER TABLE (112 HEARTS) ; THIS INCLUDES AGES 41-50 ONLY

NUM- BER	AGE AND SEX	HT. WT.	HISTORY RHEUM. FEVER	CARDIAC VALVES THICKENING					VASCULAR			PERIVASCULAR			POSITIVE + PROB. DOUBT. D
				FUSION COMMISS.	AORTIC	MITRAL	TRI- CUSPID	ARTERITIS "RHEUM."	FIBRI- NOID NECRO- SIS	ELASTIC TISSUE ALTERA- TION	ASCHOFF BODY	FIBRI- NOID "SWELL- ING"	CELLULAR INFIL- TRATION		
22258	41-50 F 45	440	-	-	+	+	+	+	++	++	-	++	++	+	+
S-4202	M 50	420	N.R.	-	-	+	-	+	+	+	-	+	+	+	D
S-4159	M 49	250	N.R.	+	-	+	-	+	+	+	+	++	++	+	P
S-4431	M 48	325	N.R.	-	-	+	+	+	+	+	+	++	++	+	+
S-5113	M 50	450	N.R.	-	-	+	-	+	+	+	+	++	++	+	+
24286	F 43	300	N.R.	-	-	+	-	+	+	+	+	++	++	+	+
22040	F 43	410	N.R.	-	-	+	-	+	+	+	+	++	++	+	+
25008	F 43	300	N.R.	-	-	-	-	+	+	+	+	++	++	+	+
S-5170	F 45	325	Sore throats	-	-	+	-	+	+	+	-	++	++	+	P
S-5188	M 47	325	N.R.	-	-	-	-	+	+	+	-	++	+	+	P
25655	M 41	310	N.R.	-	-	-	-	+	+	+	+	++	++	+	+
26397	F 47	300	N.R.	-	-	+	-	+	+	+	+	++	++	+	+
24416	M 45	600	-	-	-	+	-	+	+	+	+	++	++	+	+
26545	M 49	470	-	-	-	-	-	-	+	+	-	++	++	+	P
S-6081	F 45	150	N.R.	-	-	-	-	+	+	+	+	++	++	+	+
S-6429	M 50	500	N.R.	-	-	+	-	+	+	+	+	++	++	+	+
S-6397	F 46	300	-	-	-	+	+	+	+	+	+	++	++	+	+
S-6083	M 50	450	N.R.	-	-	+	-	+	+	+	+	++	++	+	+

It would require too much space to publish a complete table of 112 cases. We have therefore selected the 18 cases which fall in the 41 to 50 age group as a sample for detailed presentation (Table V). There were 10 males and 8 females. The weight of the heart is not pertinent to the present study. In only one specimen was there slight fusion of the aortic commissures, and in only one instance was there aortic cusp thickening. The mitral valve was the seat of minimal thickening in 12 hearts, or 66.6 per cent. The tricuspid was similarly involved in 4 instances. The chordae tendineae were thickened in 4 hearts, in each case in connection with the mitral leaflets. All of the rheumatic stigmas were well represented in this group except in the second case, S-4202, which is considered doubtful as regards rheumatic taint. There are 13 cases in the positive group, four in the probable, and only one in the doubtful. In 10 specimens (55.5 per cent) Aschoff bodies were found. In 2 cases sub-Aschoff nodules were present, and in 6 there were none.

The main lesions found at autopsy in each of the 112 cases were recorded on our master table. Careful analysis failed to reveal any essential relationship to the problem in hand, and therefore the autopsy diagnoses are not included in Table V. It was thought that some relationship might exist in the large group with general arteriosclerosis and hypertension, especially among those with coronary occlusion. An analysis of this group, however, revealed a slightly lower percentage of cases of coronary occlusion than was found among the autopsies at the Los Angeles County Hospital for the year 1939-40.

COMMENT

The facts presented here are interesting, but their significance is difficult to evaluate. Until our knowledge of the etiology of rheumatic fever is more complete, the interpretation of the so-called rheumatic stigmas must be more or less hypothetical. It is well established that rheumatic fever is closely associated with hemolytic streptococcus infections.^{8, 14, 15} Coburn¹⁴ reported recently that in cases of infection with hemolytic streptococci without later development of rheumatic fever, the antistreptolysin titer rises no later than two weeks after the initial infection, but, in cases of developing rheumatic fever the titers rise in the third week and remain high as long as the disease remains active. The relationship of rheumatic carditis to allergic-hyperergic inflammation has been widely accepted.^{5, 8, 9, 10, 12} Coburn¹⁴ has suggested that rheumatic fever develops in persons who, because of hereditary and environmental deficiencies, are unable to react to infections with hemolytic streptococci in the usual way. Their immune response to the primary infection is inadequate, with the result that the cells of the reticuloendothelial system become sensitized. Recurrent infections with these organisms produce in such persons the symptoms and the allergic-hyperergic tissue changes known as rheumatic fever. The majority of

the population are relatively immune to these organisms, and therefore are not subject to rheumatic infections. The hemolytic streptococci referred to by Coburn are those of the A group of Lancefield.

According to a recent survey by Paul,¹⁵ children in institutions for rheumatic heart disease tend to develop exacerbations of rheumatic carditis two or three weeks after upper respiratory infections caused by hemolytic streptococci. Jones and Mote¹⁶ report that, of 271 observed recurrences of rheumatic fever, 67 per cent were associated with infections of the respiratory tract, two-thirds of which were symptomatic sore throats. Of the first rheumatic attacks, 58 per cent were preceded by infections of the upper respiratory tract. These attacks of carditis would appear to be allergic-hyperergic reactions to the products of the hemolytic streptococci.

Assuming, with Coburn¹⁴ and others, that the hemolytic streptococcus is the etiologic agent in rheumatic fever, one may logically explain the rheumatic stigmas found in the papillary muscles and immediate vicinity of the cardiac valves by assuming that they are allergic phenomena which result from repeated streptococcal infections of tonsils, pharynx, and sinuses in persons who are able to respond in the usual way. Such repeated infections may selectively affect the cardiac valves and produce mild inflammatory responses which result in minimal thickenings of the valve edges. Certainly in the patients who develop rheumatic fever the valves are involved early and often severely. The inflammation also spreads to the myocardium but is usually most evident near the valves. In the immune patient, changes characteristic of rheumatic infection can be found, but as a rule only in close proximity to the valves. The papillary muscles, to which the chordae tendineae are attached, appear to be most affected.

Possibly the reaction is not as specific as we have indicated. Swift and his associates⁵ point out that a variety of streptococci have been isolated from blood cultures and the lesions of acute rheumatic fever. Animals sensitized to one strain of streptococcus have shown marked hypersensitivity to that particular strain, but have also been quite sensitive to other strains, as well.

If later investigations demonstrate a specific organism other than the streptococcus in rheumatic fever, the explanation offered above is still pertinent. Whatever the organism may be, it probably gains entrance through the nose or tonsils, for the majority of rheumatic infections follow upper respiratory disease.¹⁶ The so-called stigmas of the rheumatic virus discussed in this paper may nevertheless represent manifestations of allergy to repeated upper respiratory infections in persons who are relatively resistant. Just as the pleural scars at the apices of the lungs are the "vaccination marks" which indicate immunity to tuberculosis, so the minimal valvular lesions and microscopic hyperergic changes in the heart muscle indicate immunity to rheumatic fever resulting from previous subclinical infections.

SUMMARY

1. Of 124 hearts studied, 112 were free of valvular lesions as commonly understood. The remaining 12 specimens presented gross lesions of chronic rheumatic endocarditis or subacute bacterial endocarditis, or both. This smaller group constituted our controls.

2. Among the larger group of 112 hearts, minimal thickening of the mitral valve leaflets was observed 74 times (66.0 per cent). Slight thickening of aortic cusps and tricuspid leaflets was present much less often. The chordae of the mitral valve were thickened in 42 cases, or 37.5 per cent.

3. The various microscopic rheumatic stigmas were studied in blocks from the papillary muscles of the left ventricle and in some cases from blocks passing through each of the valves. All of the stigmas (arteritis, fibrinoid changes, elastic tissue alterations, Aschoff bodies, and infiltration with histiocytes) were abundantly present.

4. Aschoff bodies were found in thirty-three (29.5 per cent) instances and Aschoff-like collections in an additional 34 hearts (30.3 per cent).

5. "Positive," healed, minimal rheumatic infection was diagnosed 68 times (60.7 per cent), "probable," healed, minimal rheumatic infection, 36 times (32.1 per cent), and 8 specimens were called doubtful.

6. There was a history of rheumatic fever or chorea in 9 of the 12 patients in the control group. The rheumatic stigmas were abundant in all but one case. This patient had syphilitic aortitis, in addition to chronic rheumatic valvular disease and bacterial endocarditis.

CONCLUSIONS

1. About 90 per cent of the hearts studied revealed stigmas of rheumatic infection in the myocardium in close proximity to the mitral valve.

2. These lesions are believed to be the result of allergic-hyperergic responses to recurrent upper respiratory infections with the rheumatic virus in persons who are relatively immune.

3. The hemolytic streptococci would seem logically to fit the role of rheumatic agent under the conditions proposed. We have presented no direct evidence that this is true.

4. The present study indicates a widespread distribution of the rheumatic virus, comparable perhaps to that of tuberculosis or poliomyelitis. As a corollary to this, the greater percentage of the population is immune to the virus of rheumatic fever, just as it is to tuberculosis and poliomyelitis.

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STUDIES WITH THE BALLISTOCARDIOGRAPH IN ACUTE CARDIAC INFARCTION AND CHRONIC ANGINA PECTORIS

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HERETOFORE, the reported clinical studies with the ballistocardiograph¹⁻⁶ have been widespread surveys to gain experience with the common deviations from the normal. This, our first study of a specific disease by this method, deals with the coronary type of heart disease and includes studies made both during the acute stage after cardiac infarction and in cases of chronic angina of effort. There have been very few studies of the amount of the circulation in these conditions,^{7, 13} probably because many of the patients are too ill to permit the application of the older cardiac output methods. Therefore, we planned to estimate the amount of the circulation in many cases of coronary heart disease and hoped to be able to gain information beyond the scope of the methods which are routine in most hospitals.

Since 1937, about 1,600 ballistocardiograms have been made on subjects at the University Hospital, chiefly from the medical wards. Among these were 106 records on 55 patients with angina pectoris or cardiac infarction. All of these patients had been examined by one or both authors, and most of them had been directly under their care. To avoid unconscious bias, all the records were reviewed and classified by one of us (F. C. W.) without knowledge of their ballistocardiograms. The comparison of the clinical aspects, as observed by one author (F. C. W.), with the ballistocardiograms, as analyzed by the other author (I. S.), and the conclusions that can be drawn therefrom, form the subject of this paper.

The results indicate that profound abnormalities of the amount of the circulation, sometimes accompanied by alterations of impact form, are commonly, but not invariably, found in coronary heart disease. The data show that these abnormalities may develop and recede during the acute period after cardiac infarction, but that they are found with greater frequency and severity in cases in which there is a long history of angina pectoris.

METHODS

Apparatus.—The principles and construction of the ballistocardiograph, the apparatus used to secure records of the heart's recoil and the blood's impacts, have been described.¹ Nothing is required of the patient except that he lie relaxed and motionless on the table, so that the method is well adapted for the investigation of ill persons.

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Taking records.—Estimations of blood pressure and all ballistocardiograms were taken while the subjects lay on their backs in the horizontal position, after a rest period of at least fifteen minutes, and never within two hours of a meal. The acutely ill patients were brought to the ballistocardiograph room in their beds and lifted directly from the bed to the table. Electrocardiograms were occasionally taken simultaneously with the ballistocardiograms by projecting the string's shadow on the same film, but more frequently they were taken in the usual manner within a few days of the corresponding ballistocardiograms.

Reading the records.—Typical examples are given in Figs. 2 and 5, and it is well to precede the details of record analysis by several general statements.

Since any movement made by the patient affects the record, artifacts are common, and only the constantly repeated features deserve any attention.

With reservations to be discussed, the amplitude of the systolic waves is related to the absolute value of the cardiac output, but large persons naturally have a greater amount of circulation than small ones, so that the decision concerning what is normal rests on the relation of the cardiac output to the size of the person. Also, older persons, even though they are healthy, give smaller impacts than their juniors. Moreover, if the impact form is abnormal, there are data to support the belief that the cardiac output may be larger than the amplitude suggests. Therefore, the record of one person may not necessarily be directly comparable with that of another, but records obtained on the same person at different times are directly comparable.

The decision concerning normal ballistic form.—The first step in the analysis of any record is to decide whether the form is normal or abnormal; diagrams of both kinds are shown in Fig. 1. The normal can be recognized at a glance, and attention should be concentrated on the I and J waves, for, from their areas, cross-hatched in the figure, the cardiac output is calculated. Sharp and well-defined I and J waves have been found in all the records on healthy persons, and in a great majority of those on patients. They are caused by the recoil from, and the impacts of, the blood moved by systolic ejection. The other features of normal records on healthy persons are less constant. Just before ejection an upward H wave usually occurs, and, especially if the rate is slow, this may be preceded by a complex of small waves which, since they resemble the impacts after isolated auricular contractions in heart block, are probably caused by motion of blood imparted by auricular contraction. But this feature is not well marked in all normal subjects, nor is this part of the record always flat in auricular fibrillation, so that other factors must enter in. During diastole a series of small waves occur; these are attributed by Hamilton⁸ to standing waves in the aortic blood, for they coincide with aortic pressure waves. We have data to support this interpretation in some cases. Always much smaller than the normal systolic complexes, these waves vary in amplitude in healthy persons and are almost absent in some.

The size of the normal complexes always varies with the phases of respiration; it increases during inspiration and diminishes during expiration.

The common types of abnormality can easily be recognized by comparison with the diagrams of Fig. 1, but it must be kept in mind that those shown are extreme examples, and that complexes whose shape lies between such forms and the normal are encountered more frequently.

Analysis of records with a normal form.—When the form was normal, cardiac output was calculated by the area method.² No claim has ever been made that the value obtained is highly accurate; indeed the absolute accuracy of all cardiac output methods is unknown. Nevertheless, results in individual cases are readily reproducible, the characteristics of normal records are well known, and we have no doubt that the major deviations from the normal which are found in so many cases are significant.

The values for cardiac output per minute, per unit of body weight, will be expressed as percentage deviations from the average normal; the normal limits are

± 22 per cent. When thus expressed, the application of the correction of Cournaud, et al.,⁹ which adjusts for the underestimation of the size of the living aorta, from tables based on data obtained at necropsy, does not alter the result because both normal and abnormal values are changed proportionally.

One of the aims in estimating cardiac output is to gain information concerning the heart's work and so obtain evidence of its strength or weakness. Because the pulmonary pressure is unknown, only the work of the left ventricle can be estimated, and, leaving out the velocity factor, which is negligible in most resting subjects, this work is approximately equal to the mean blood pressure, in mm. Hg. times the specific gravity of mercury, 13.6, times the cardiac output. Normal standards for left ventricular work per minute per pound of body weight have been compiled from a series of healthy persons, 57 men and 48 women, between the ages of 20 and 40 years. Using Cournaud's correction,⁹ the ventricular work per minute per pound of body weight of healthy young adults averages 36.0 Gm. meters for men and 34.0 Gm. meters for women; the standard deviations are 5.2 and 5.6 gram meters, respectively. Combining these values, we obtain an average normal of 35.0 Gm. meters per minute with the usual statistical limits of normal, i.e., twice the standard deviation, 30 per cent above and below this figure. Data obtained by the ethyl iodide method on 31 normal persons yielded almost identical values.¹²

It must be noted that the standard deviation of the left ventricular work is about one-third larger than that of the cardiac output of healthy persons. This means that the work of the heart among healthy persons scatters over a wider range than the cardiac output. Therefore, the normal limits for work are considerably wider than those for output, and larger differences are required before the work of any patient can be considered abnormal.

Analysis of records with an abnormal form.—In 17 of the 106 records, the form was so abnormal that we were unable to estimate cardiac output with enough confidence to give it a numerical value. Records *b*, *c*, *d*, *f*, and *g* of Fig. 2 are examples of the abnormal types encountered. Most of the 13 abnormal records resembled *b* or *c*, and in these the amplitude was so low that a subnormal cardiac output may be properly inferred, although an exact value should not be given. Nevertheless, the bulk of our discussion will be centered about the 89 records of normal form.

In a few records, as *c*, Fig. 2, the abnormality is confined to a part of the respiratory cycle. In these we have usually calculated cardiac output from the largest and smallest normal systolic complexes, and we do not believe that the error of so doing would be large. Again, the amplitude of such records is always so small that only the degree of the "*hypokinemia*" could be in error.

The terms "*hyper*." and "*hypokinemia*" will be used to express the corresponding abnormalities of the amount of the resting circulation under the conditions of our tests. For convenience of expression, the left ventricular work of resting patients under the conditions of our experiments will often be referred to as the cardiac work, without further qualification.

Criteria used in classification of patients.—The criteria which Wood employed were such that doubtful cases of coronary heart disease would be excluded from our series, even though some real cases were probably also eliminated.

The diagnosis of chronic coronary disease was based upon: (1) The presence of typical angina of effort for at least several months; (2) our knowledge that a definite cardiac infarction had occurred previously; and (3) the presence of typical electrocardiographic signs of healed anterior or posterior infarction, together with a history suggesting former cardiac infarction. A rough classification of the severity of the condition was made by dividing the cases into mild, moderate, and severe on the basis of exercise tolerance, as ascertained by questioning, not by direct testing.

The diagnosis of *acute* coronary occlusion was based upon the occurrence of an attack of pain followed by either (1) the typical electrocardiographic pattern of one of the recognized types of cardiac infarction, or (2) progressive changes in the electrocardiogram which were not the result of drug administration or any other obvious cause except infarction. The cases were classified as mild, moderate, or severe according to the degree and duration of the fever and leucocytosis which followed the attack, the severity and duration of the pain, the diminution of the blood pressure, and the occurrence of shock or failure.

Selection of cases.—In aortic regurgitation, as part of the blood expelled in systole reenters the heart in diastole, the amount of the circulation cannot be estimated from the ballistocardiogram. Therefore, such cases were not studied, and the well-known group with angina pectoris secondary to syphilitic aortitis is not represented in our data.

RESULTS

Abnormalities of Ballistic Form in Coronary Disease.—Records showing abnormal ballistic forms were encountered in 17 instances. Most of these were obtained from patients with symptoms of over three years' duration, although, because of an acute attack shortly before, some of them are classified as acute in Table I.

The characteristic "late downstroke" type, diagrammed in Fig. 1b, was encountered infrequently. The record of R. J., Fig. 2g, who suffered from biliary tract disease and later from pain characteristic of angina pectoris during effort, is a classic example of this type, but we have no similar case in our series. Forms intermediate between this and the normal, i.e., shallow I waves and retarded J peaks, were seen occasionally.

The "late M" type is diagrammed in Fig. 1c, and similar records on patients with coronary disease were reproduced in a previous publication.² Attributed to a ballistic imbalance of the two sides of the heart, we had wondered if this abnormality would be found to be characteristic of cardiac infarction, but this has not proved to be so. The expectation based on theory has been weakened by the realization that, for anatomic reasons, movement of the blood in the systemic arteries plays a far larger part in the genesis of impacts than movement in the pulmonary system.¹⁴ Also, our larger experience has not borne out our early observations, partly because we have become more strict in interpreting the records. Those like the third record of patient H. B., shown in Fig. 2, j3, we might have previously accepted as the late M type, but the second apex of the M is small and occurs after systole is over, so that it is probably an after-vibration, i.e., a large "L" wave. It is the lack of the second after-vibration, the "N" wave, which makes the record look unusual. Typical "late M" tracings (Fig. 2f) are certainly to be found in coronary heart disease, but they occur infrequently. Since in many cases of cardiac infarction only a small proportion of the total ventricular muscle is found to be damaged at necropsy, it seems reasonable that the blood might be ejected with a normal velocity curve in many resting subjects with small lesions, especially if cardiac output has diminished.

A third type of abnormality is the "early M" type, shown in Fig. 1*d*; the first limb of the M is an exaggerated H wave. Records of this type are sometimes hard to distinguish from "late M" records without additional evidence of the exact position of systole, which we obtained by a simultaneous electrocardiogram whenever we were in doubt. The second record of H. G., Fig. 2, *d2*, is a conspicuous example of this type, and we have three other records in cases of coronary disease which resemble it. Although less conspicuous examples occur in hypertension, the extremes of this abnormality have all been found in records from patients with recent infarction.

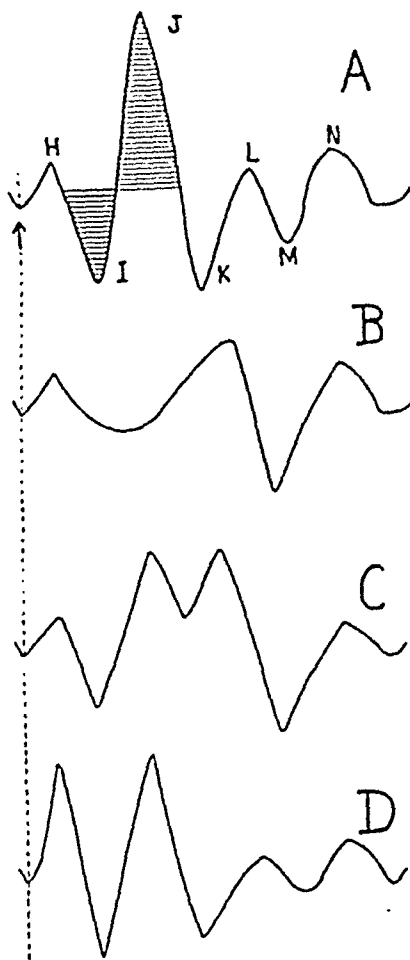


Fig. 1.—Diagrams of the normal ballistocardiogram and extreme types of the abnormalities of form, aligned by the arrow and dotted line at the beginning of ventricular systole, as shown by the electrocardiogram.

A. Commonest type of normal record. The wave areas used to estimate cardiac output are crosshatched. The letters are those given to the corresponding peaks and valleys.

B. The "late downstroke" type. The downstroke late in systole is the most conspicuous feature of these records.

C. The "late M" type. The first apex of the M corresponds to the J wave in the normal record. This form is interpreted as a combination of the two preceding records, A and B.

D. The "early M" type. The abnormality is an exaggeration of the H wave of the normal record, and the second apex of the M is the J wave.

Fig. 2.—Ballistocardiograms from patients with chronic coronary heart disease, illustrating the abnormalities of form, contrasted with the normal, and records obtained in a single case over a period of years. The records are reproduced three-fifths their original size.

To aid readers in interpreting the records the time of the beginning of ejection of blood from the heart has been marked by a line underneath the records. In records of 1 and 2, and 6, the placing of this line was assisted by an electrocardiogram which was recorded on the same film as the ballistocardiogram. There was little doubt about the placing of ejection in the other records, except *B*, in which the amplitude is so small and the form so confused that systole cannot be identified with confidence.

at A normal record for comparison with the abnormal records below, taken on the senior author, aged 46 years, height 6 feet, weight 185 pounds.

b: Record of *B. K.*, aged 51 years, height 5 feet, weight 119 pounds. Coronary occlusion eleven years before, angina after effort since that time. Blood pressure, 180/90, heart normal in size by orthodiagram. Anginal attacks now occur while she is in bed. Given paravertebral alcohol injection the day after this record was taken. A ballistocardiogram one week later showed no improvement. Note the small amplitude of the ballistocardiogram.

c: *H. G.*, aged 62 years, 5 ft. 1 in., 140 lbs. Blood pressure 175/92. Angina after effort for at least six years. The story was a little suggestive of acute infarction four days before this examination, when she had a changing electrocardiogram, but it was not diagnosed. Note the tiny ballistocardiogram.

d: *H. G.*, aged 55 years, 5 ft. 10 in., 164 lbs., blood pressure 110/70. First record, four days after anterior infarction, with characteristic electrocardiogram. At this time there was auricular fibrillation with a ventricular rate of 148. Note the large amplitude and the varied ballistic forms that are always seen in auricular fibrillation. Second record, eight weeks after infarction, blood pressure, 112/70, normal sinus rhythm. Note the early M shape of ballistic record. This patient died of liver abscess and septicaemia five months later. Necropsy confirmed the diagnosis of infarction.

e: *S. K.*, aged 51 years, 5 ft. 5 in., 174 lbs., blood pressure, 114/86. Record obtained four months after posterior infarction, with characteristic electrocardiogram changes. There was no angina during the acute period, but the patient had recurring pain after effort and even in bed, and was still bedfast when this record was made. Note the small ballistic amplitude and the abnormality of the J wave in the smaller complexes of the respiratory cycle, where the J peak is flattened, notched or notched. The larger complexes are normal in form.

f: *J. B.*, aged 49 years, 5 ft. 1 in., 135 lbs., blood pressure, 118/80. Probably posterior infarction two years before, with angina after effort thereafter. Anterior infarction eight weeks before this record, recovering slowly. Note "late M" form over most of the respiratory cycle.

g: *R. J.*, aged 64 years, 5 ft. 9 in., 173 lbs., blood pressure 112/75. Formerly, chronic cholecystitis and cholelithiasis. Gall bladder and stones removed seven years before this record. History of attacks of subternal pain after effort for the preceding two months. Electrocardiogram practically normal. Note the late downstroke type of ballistic record.

h: *L. H.*, aged 57 years. In 1937, 5 ft. 8 in., 170 lbs. This man, examined as a healthy person in 1937, later developed angina and died of infarction (see text). Note small amplitude, especially in the smaller complexes.

i: *K. V.*, aged 74 years. In 1937, 5 ft. 3 in., 120 lbs. This woman, examined as a healthy person, developed angina four years later. She is living and active at present, age 79 years.

j: *H. B.*, aged 60 years, 5 ft. 5 in., 167 lbs. First record in 1937, when supposedly healthy. Note low amplitude. The rapid camera speed makes this record appear more different from the following than it actually is. Second record, 1938, six weeks after posterior infarction, mild course. Note low amplitude and flattening of J waves in smaller complexes. Third record, 1940, working steadily and effectively as an orderly, admits angina after unusual exertion. Note larger amplitude. The vague M shaped appearance is misleading; the second apex of the M is in diastole, the systolic form is normal. Fourth record in 1941. Angina occurs on less effort. He is now unable to work effectively and has lost his job. Note smaller amplitude than previous record.

k: *K. N.*, aged 53 years, 6 ft. 2 in., 208 lbs., blood pressure, 116/75. He had myocardial infarction with severe symptoms about two years before this record was made, and almost died of embolism; femoral embolectomy was required. At the time of this test, clinical recovery was practically complete and he was working hard. At time of writing, one year later, he has had no further trouble. Note that the ballistic record is completely normal.

l: *E. D.*, aged 60 years, 6 ft., 173 lbs., blood pressure, 165/70. This man had myocardial infarction with mild symptoms about one year before this record was taken. No residual symptoms were admitted. Note that the ballistocardiogram is entirely normal. At time of writing, three years later, he is working hard at the practice of medicine and has had no further trouble.

In confirmation of the observations of Tennant and Wiggers,¹⁰ one of us (Wood) has often noted that, when a dog's coronary artery is ligated, the area of the heart which is deprived of its normal circulation soon begins to bulge with each systole. Such a weak spot in the cardiac wall near the apex, bulging when systole begins, should cause a displacement of the center of mass of the heart's blood downward until ejection took place. The recoil from this movement would throw the body headward and cause the ballistic II wave to be increased in

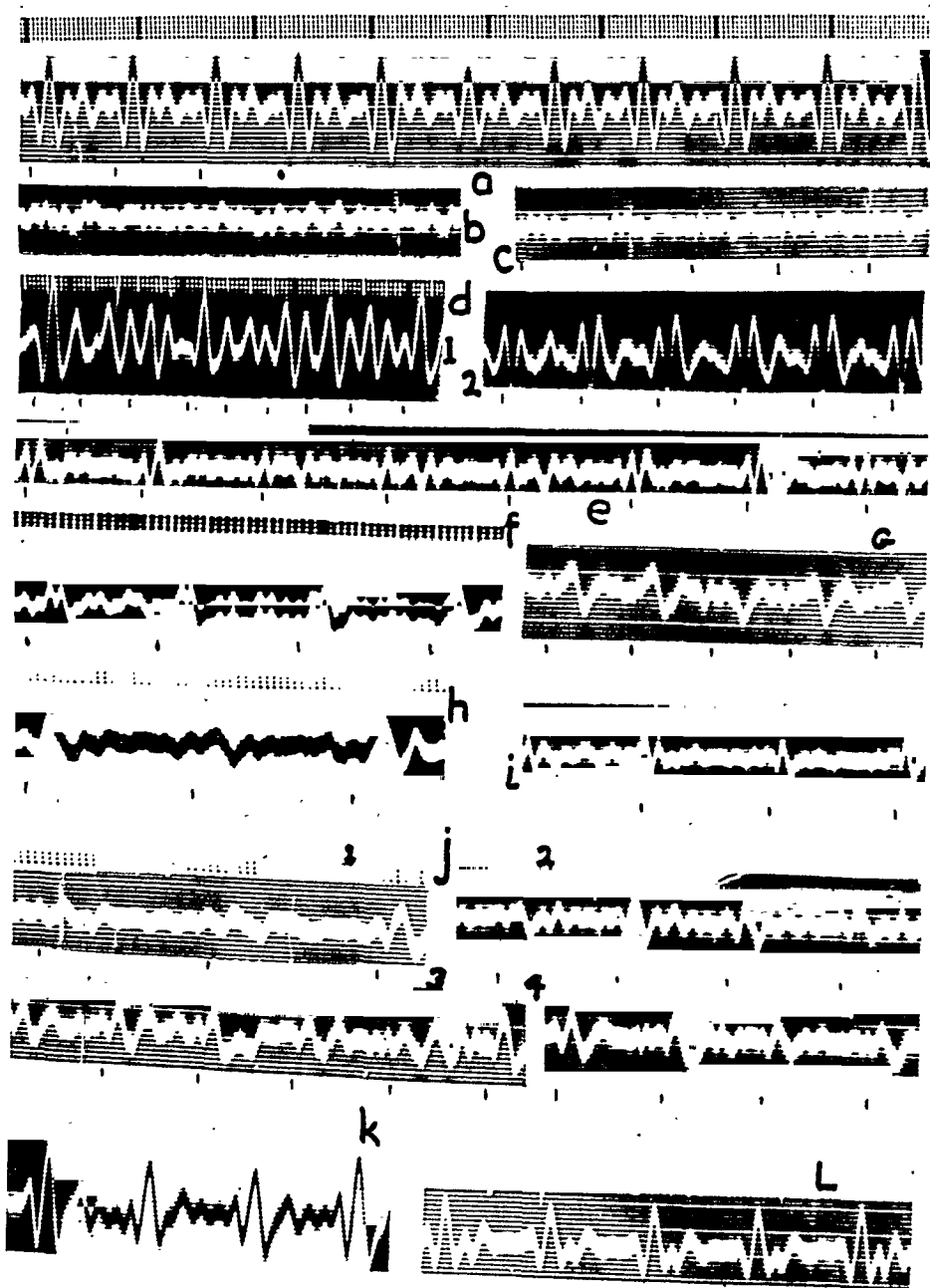


Fig. 2.—(For legend see opposite page.)

size. We have not performed animal experiments, however, to support or disprove this speculation.

A fourth type of abnormality was encountered most frequently in this study. In it the whole ballistocardiogram is so greatly reduced in amplitude that the individual waves are hard to identify, and the details of form are correspondingly uncertain. The record of patient E. K., Fig. 2c, is of this type, and we have found similar records in nine other cases.

In addition to these extreme types, we have numerous records in which an abnormality of impact form was confined to the smaller complexes of the respiratory cycle; the record of S. K., Fig. 2e, is an example.

When the records were of the early M type we calculated cardiac output from them in the usual manner, but when the form is of the late M, or late downstroke, type, the ordinary criteria for estimating cardiac output may not be applied. Rather than use criteria concerning whose accuracy we have little knowledge, we have not given a numerical value to the cardiac output estimated from any of these abnormal records, so that their data do not appear in the charts. Nevertheless, the amplitude was usually so small in these cases that we feel justified in the belief that the circulation was very subnormal. Nothing has been found among these abnormal records which is inconsistent with the results to be reported quantitatively.

Estimations of Cardiac Output and Work in Coronary Heart Disease.—The statistical analysis is given in Table I. Unfortunately the number of cases is too small to permit fine distinctions.

TABLE I

STATISTICS IN ACUTE CARDIAC INFARCTION AND CHRONIC ANGINA PECTORIS

		NO. OF CASES	NO. RECORDS IN ABNORMAL FORM	CARDIAC OUTPUT		L. V. WORK	
				MEAN DEVIATION FROM EXPECTED NORMAL	STANDARD DEVIATION ABOUT THE MEAN	MEAN DEVIATION FROM EXPECTED NORMAL	STANDARD DEVIATION ABOUT THE MEAN
Acute							
Severity	Mild	9	2	-33%	5%	-20%	10%
	Moderate	12	3	-17%	3%	-17%	6%
	Severe	6	2	-17%	9%	-20%	10%
Chronic							
Severity	Mild	6	0	-13%	8%	0%	12%
	Moderate	6	1	-43%	7%	-25%	11%
	Severe	16	4	-35%	4%	-32%	4%

In acute coronary occlusion the average work of the heart is not significantly correlated with severity, as judged by the symptoms. To our surprise, in mild cases there was a smaller average cardiac output than in patients with more severe symptoms. When the data from mild cases were compared with those of the moderate group, this difference was significant, but, when compared with the smaller number of severe

cases, no statistical significance was apparent. But it must be remembered that complicating factors, such as pain, apprehension, and fever, enter into the results in acute infarction. Also, some patients whose disease was classified as mild because the acute attack produced few symptoms at rest had suffered from severe angina of effort for many years. Such patients may have had a larger proportion of their myocardium destroyed than was the case among those who had infarction without any antecedent history of coronary disease. Also, data obtained both soon after infarction and during convalescence are included in the analysis. The group lacks homogeneity, and it is not surprising that the statistics are uninforming.

The results in the chronic group were more in accord with expectations, for the average resting cardiac work was directly related to exercise tolerance. The difference between the cardiac work when exercise tolerance is little reduced, and the values obtained when it is moderately or greatly reduced, are highly significant, and this statement applies to the output, also. The difference between the values among those with moderate, and those with great, reduction of exercise tolerance does not attain statistical significance.

Considering the data as a whole, one sees that the averages of both work and output are far below normal in coronary disease, and they are more reduced in the chronic than in the acute stages. Of the two, output is more reduced than work. But, as is shown by the standard deviations, the scattering of the data is considerable. The averages, therefore, do not merit too much attention, and the analysis of individual cases gives a more interesting picture.

Studies in Acute Cardiac Infarction.—By good fortune we examined patient E. D. about two weeks before, as well as after, cardiac infarction and the results are shown in Fig. 3. Syphilis, never adequately treated, had been diagnosed three years before, but there were no clear signs of aortic regurgitation, and the diagnosis of arteriosclerotic heart disease was preferred. Symptoms strongly suggesting angina of effort had been present for a month, and it was thought that cardiac infarction might be in the offing; this led to admission to the hospital, where a ballistocardiogram was secured. Two weeks later he had a severe attack of substernal pain which lasted about twenty-four hours and was not relieved by nitrites. Fever, leucocytosis, and more rapid sedimentation of erythrocytes followed, and typical electrocardiographic evidence of recent anterior infarction developed. Six days after this incident his blood pressure was lower, and a ballistocardiogram showed that the circulation had also diminished; the left ventricular work per minute had declined 33 per cent. Estimations made during the next few weeks showed that the changes in cardiac output and blood pressure were small and in opposite directions; the work remained about the same. The smallest circulation was found during the fourth week, when the only estimation below the lower normal limit was obtained; at this time

the blood pressure had recovered somewhat. After this, uneventful clinical recovery was accompanied by increased circulation, but the original blood pressure was not regained, and, at discharge, the left ventricle was calculated to be doing 20 per cent less work than before the infarction.

The observations in this case are consistent with those in most other cases; the records and data of one such case are given in Fig. 4. In Fig. 3 are charted the values for cardiac output and work in the twenty-

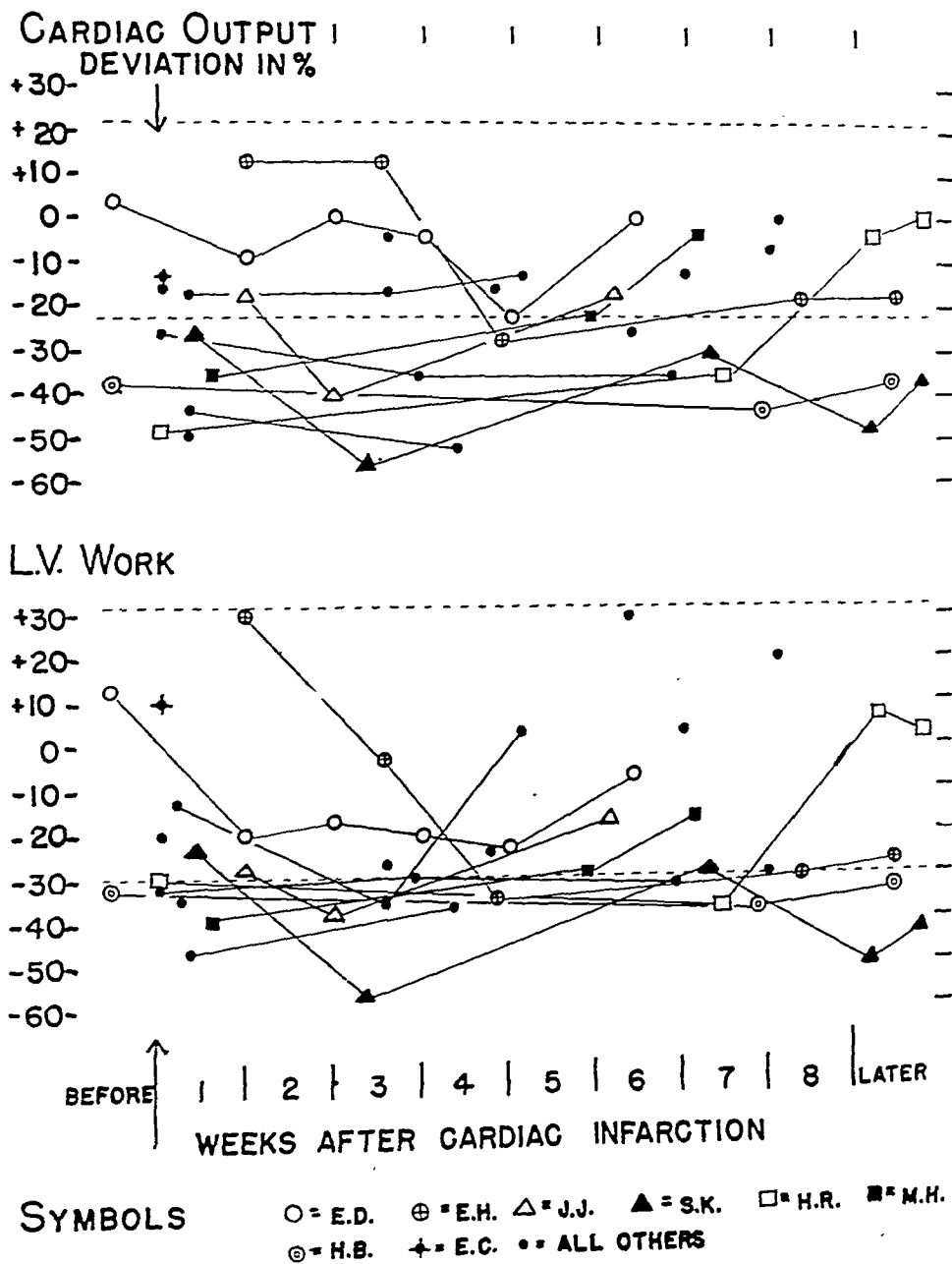


Fig. 3.—Cardiac output and left ventricular work, chiefly in the first eight weeks after acute cardiac infarction. The data obtained in the eight weeks after this event are plotted according to the time in days. All data obtained before infarction, or later than the eight weeks after it, are plotted without regard to time. Values obtained from the same subject are connected by solid lines.

The horizontal dotted lines indicate the statistical limits of the cardiac output and left ventricular work of normal subjects, and are placed at a distance of twice the standard deviation from their mean. The values of 95 per cent of healthy persons will be found within the dotted lines.

one cases in which we obtained ballistocardiograms of normal form during the eight weeks after cardiac infarction. Obviously, both cardiac output and work tend to diminish during the first four weeks; this trend was absent only in those cases in which we found unusually low values at the first test; in these the diminution may have already taken place.

After the fourth week, clinical improvement was accompanied by a return of the circulation and work toward normal, and all, except two patients, were discharged in reasonably good condition. Patient E. C. died during the first week, and S. K., after restoring his circulation and work part of the way toward normal, failed to hold the gain. The clinical course of the latter corresponded to these observations, for angina on very little effort confined him to bed on discharge, and, when readmitted two months later, he was no better.

E. H. AGE 59 WT. 140

2-1 ANTERIOR CARDIAC INFARCT

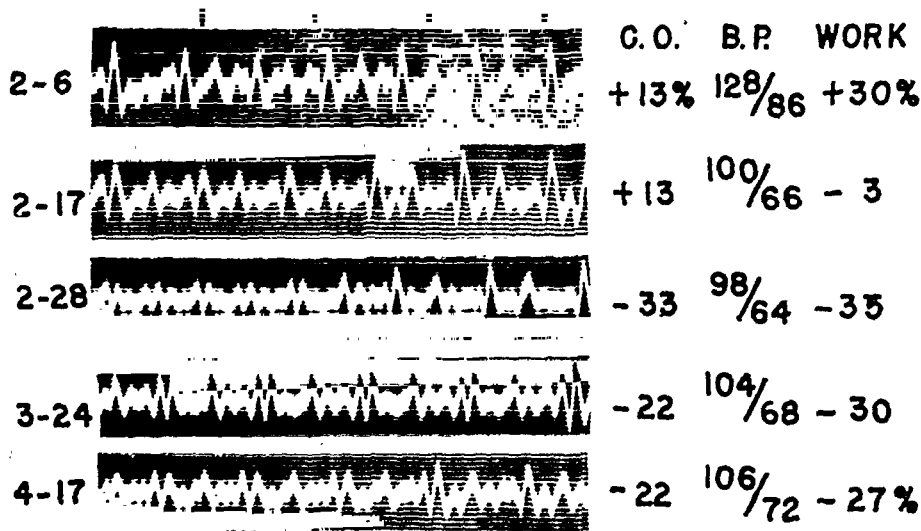


Fig. 4.—Ballistocardiograms obtained on the same subject during the acute stage of cardiac infarction, with the calculated cardiac output, blood pressure, and left ventricular work. The records have been reduced to three-fifths actual size. The time record at the top applies to all; the longest interval is one second.

On the Course of Chronic Coronary Heart Disease.—The records of a patient who was followed for 4 years are reproduced in Fig. 2j. H. B., a hospital orderly, was first examined in 1937 in the general roundup of supposedly normal persons during the study which determined the normal standards. To our surprise the cardiac output was far subnormal, although the subject admitted no symptoms at the time. A typical, although mild, attack of posterior cardiac infarction occurred a little over a year later, and the second record was obtained six weeks after this event, just before he was ready for discharge from the hospital.

The circulation was still far below normal at that time. The patient made a good clinical recovery, lighter work was found for him, and he worked steadily for the next few years, although he had angina after unusual effort. The third ballistocardiogram, taken 20 months after the infarction, showed a little improvement in the circulation, but it was still far from normal. The gain was not maintained, angina appeared after less and less effort, and fifteen months later he was discharged as unable to do the work required. At this time the circulation was again found to be extremely subnormal.

Several points about this experience are illuminating. First, an abnormality of the circulation was discovered early in the course of the disease before symptoms were admitted, and well over a year before acute infarction was diagnosed. Second, after recovery from the acute symptoms the cardiac output was lower, but very little lower, than before. Third, some recovery took place, and, finally, this recovery was not maintained. Our other evidence on these points will now be taken up.

The Circulation Early in Coronary Heart Disease.—During 1937 and 1938, two hundred healthy persons of all ages were examined on the ballistocardiograph as part of the study to determine the normal standards. Fifty-six of these persons were over 50 years of age. Eleven of these persons, all men but one, proved to have hypokinemia. The after-histories of these eleven patients are of great interest because five of them developed clear evidence of coronary heart disease in the years which followed.

Most of these subjects were either physicians or other professional persons employed in the Medical School, and none of them admitted symptoms when tested in 1936 to 1937. Nevertheless, the obvious conclusion that we had detected an abnormality of the circulation before the development of symptoms of coronary disease was weakened by the discovery that one subject had failed to inform us of a mild coronary attack, accompanied by electrocardiographic changes suggesting a small infarct, which had occurred two years before. Reticence about such ailments is very characteristic of physicians, and it is conceivable that the others might have had more trouble than they admitted; moreover, those who were not physicians may have failed to interpret their sensations properly. Thus we are not certain that a ballistocardiographic abnormality preceded the appearance of symptoms, but it did precede "recognized," or at least "admitted," symptoms in several subjects.

F. D., aged 69 years, with a circulation of -35 per cent in 1937, had mild angina on considerable effort about a year before his death in an accident at the age of 73 years. F. G., aged 59 years, who failed to admit evidence of infarction in 1935, had a circulation of -39 per cent when first examined in 1937. At that time he appeared to be in good health, but he has had at least one small cardiac infarct since. He made a good recovery and is working actively at present.

K. V., a "healthy" woman, who had a subnormal circulation (Fig. 2i) when examined in 1938 at the age of 74 years, developed mild, transient, substernal pain on rapid stairclimbing at the age of 78 years. The attending physician believes this to be angina. The patient continues to be extremely active for her years; she works for hours at a time in her flower garden, and the condition is evidently extremely mild.

I. G., aged 57 years, was also examined as a healthy person in 1937. At that time his circulation was -35 per cent. The course of the case was complicated, and the patient, a physician, was not communicative about his troubles. A renal calculus was removed at operation in 1940. An infection with *Brucella abortus* incapacitated him for over a month in 1941, and he never altogether recovered his health. Anginal attacks were first observed by the attending physician about three months before death, in 1942. The last illness began with pneumonia, complicated later by empyema which was surgically drained. He was rallying from this when he died quite suddenly. Necropsy showed an infarct of the lateral wall of the left ventricle which was judged to be several days old. There was marked, widespread arteriosclerosis, including the coronaries.

Although coronary heart disease has developed in a considerable percentage of older persons with subnormal circulations, it has also developed in subjects in whom we failed to demonstrate any abnormality of the circulation. C. N., a man, aged 48 years when examined in 1937, had a circulation of -13 per cent; this is well within normal limits, although below average normal. He had typical cardiac infarction in 1941. The course was mild and he made a good recovery. Six months later his circulation was -22 per cent, at the lower limit of normal.

It should also be noted that the circulation of E. D. (Fig. 3) was normal during the period of premonitory symptoms that preceded a cardiac infarct.

The Circulation and Cardiac Work Late in Chronic Coronary Disease.—In Fig. 5 are plotted all the data obtained in the chronic stages of coronary heart disease. Included in this group are all patients who had had infarction in the past, irrespective of whether definite angina followed it, and all cases of angina pectoris, irrespective of whether infarction was diagnosed previously; but all values obtained within eight weeks after infarction have been omitted. Multiple values obtained in any one year have been averaged; the results have been plotted according to the duration of the symptoms.

The cardiac outputs of these patients (Fig. 5) are below normal in the great majority of instances. There seems to be a slow trend downward as the disease advances.

When the left ventricular work is studied, the proportion of the cases within the normal range is larger, almost one-half; this is the result, in

part, of the inclusion of three cases of hypertension. Many such patients, when the heart is hypertrophied and not failing, have a higher basal cardiac work than normal persons. The fact that the work of such hearts, after the development of coronary heart disease, is within normal limits does not mean that the work is not less than it was before coronary disease manifested itself. To judge such cases we need a separate "normal" standard for cardiac work in cases of hypertension, and the data are not yet sufficient to supply it.

In spite of this difficulty, the tendency for the work of the heart to diminish as the disease advances is quite obvious from the data in Fig. 5.

Anginal-like Attacks With Biliary Tract Disease.—Four of our patients who were thought to have angina pectoris also had biliary tract disease. Their data have been given an identifying mark in Fig. 5, and have not been included in Table I. Each had a long history of attacks of substernal pain on exertion, relieved by nitrites. In three patients the electrocardiogram showed little or nothing abnormal, in one it showed the signs of former anterior infarction. In all four cases, the ballistocardiogram indicated a profound depression of the circulation. In each there was evidence of gallbladder disease, and each had been subjected to an operation on the biliary tract, at which time abnormalities were discovered and corrected. In spite of this, attacks of substernal pain persisted in two of the cases, although in one (S. L.), exercise tolerance was improved after the operation. In the third case, anginal-like pain began several years after the operation. The fourth patient had had no pain since her operation, but she was last seen only a month later and had taken no exercise.

The diagnosis of angina might be challenged in these cases, and, indeed, there is never any objective proof of this diagnosis, even at necropsy. But the extraordinary abnormality of the circulation, namely, -39 per cent, -52 per cent, and -48 per cent, respectively, in three of the cases, and the abnormal form of the fourth ballistocardiogram (Fig. 2g) indicated a definite abnormality of the cardiovascular apparatus in these patients. That this abnormality may have been directly related to the biliary tract disease was suggested by the reproduction of anginal-like pain and circulatory depression when fluid was injected into the common duct in one case.⁵ Evidently we are learning more about the association of angina with biliary tract disease, an association which has long been recognized by clinicians.

DISCUSSION

Physiologic Considerations in Acute Myocardial Infarction.—

Adaptations to the disability: Although normal values for cardiac output were found frequently during the first week after infarction, at some time between the second and the fifth week subnormal values were present in almost all of our cases. Enough experience is available to convince us that simple rest in bed, on a restricted diet, will not cause

changes of this magnitude. Thus the hypokinemia may well be an adaptation to the cardiac disability which results from infarction.

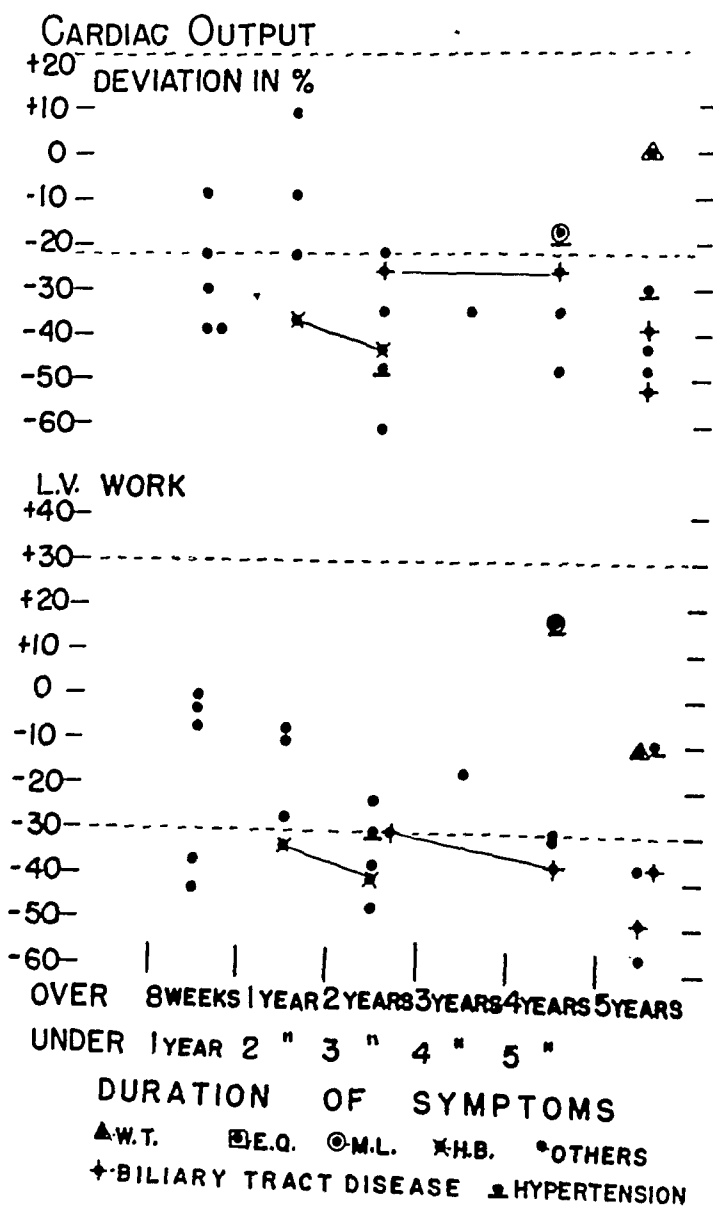


Fig. 5.—Cardiac output and left ventricular work in chronic coronary heart disease, except in the eight weeks after infarction. The horizontal dotted lines represent the limits of normal, as in Fig. 3.

As far as one can see, the best physiologic compensation for infarction of the left ventricular wall would be to reduce the work of the left ventricle. This would diminish the metabolic demands of the tissue about the infarct, where the circulation is reduced but not abolished, and so might permit this area to survive until the development of collateral circulation and the canalization of the thrombus could restore its blood supply. Theoretically, the work of the left ventricle could be reduced

by diminishing the output of blood or the resistance to this output, i.e., the general blood pressure, but there are theoretical disadvantages in so doing. Diminution of circulation has long been believed to favor intravascular clotting, so that compensation by this means would favor the formation of mural thrombi when the endocardium was involved, and so lead to embolism. One might also suppose that a sluggish circulation would favor extension of the coronary thrombus, but one of us (Wood) has examined the necropsies in a large number of cases of cardiac infarction without obtaining evidence that extension of this thrombus had ever occurred.

To diminish the work of the heart by reducing the blood pressure courts trouble in another direction, for the diastolic pressure is the main driving force of the coronary circulation, and to decrease it too much might put that circulation in jeopardy at a time when its adequate maintenance is vital.

Evidently, patients with cardiac infarction must steer a course between dangerous alternatives, and not all of them take the method which, in the light of present knowledge, seems most promising.

The results obtained in one case (H. G., omitted from Fig. 3 because of abnormal ballistic form) differ from our other experiences. These records are reproduced in Fig. 2 *d*. These records, taken simultaneously with an electrocardiogram when cardiac pain was present four days after the acute cardiac infarction, show auricular fibrillation with a ventricular rate of 130. Although any estimate of the circulation is rendered less accurate by the varying abnormalities of ballistic form which always occur with auricular fibrillation, there is no doubt that the cardiac output and work were far above the normal for a man of this age and weight. Normal rhythm was resumed spontaneously, and a second record was obtained five weeks later. This ballistocardiogram is characterized by extraordinary H waves of the early M type. Again the circulation, although smaller than before, was still above normal, but the work had diminished to a level within the normal range. Six months later this patient died of liver abscess and septicemia; necropsy demonstrated the old infarct in the anterior part of the left ventricle.

In this case, during the acute symptoms, the work of the heart was increased. Factors which might stimulate the circulation after cardiac infarction are pain, apprehension, and fever. These might explain the hyperkinemia in the first of these tests, but not in the second, when convalescence was well established. Therefore, one can hardly deny the possibility that other factors were at work.

The question why, in this case, the work of the heart was increased is related to the question why, in other cases, it was not decreased. E. C., our only patient to die during the first week, gave normal values for both cardiac output and work when tested three days before death. A large infarct on the posterior surface of the left ventricle was demon-

strated at necropsy. One wonders why more rest was not provided for this heart. This patient, however, had suffered from diabetes and moderate hypertension for many years. The blood pressure after the infarction was within normal limits, so that considerable reduction in the work of the heart may have taken place before our test was made.

Studying Fig. 3, one wonders why it took several weeks for some patients, e.g., E. H., to reduce their work to a minimum. No answer can be given to this question, but it should be recalled that the maximal physiologic adaptation to the lower oxygen supply at high altitudes requires several weeks. Perhaps when the tissues lack oxygen because of diminution of the circulation, time is required for full adaptation.

Another factor in this slow reduction of work is the behavior of the blood pressure. That blood pressure diminishes after cardiac infarction is well known, and no detailed description of our data is required. Subnormal values were found soon after the infarction in some cases; in others a much more gradual decline occurred. This reduction did not always run parallel to the diminution of cardiac output, and so was not the result of change in the latter. It should be considered another adaptive mechanism.

Relation of cardiac work to pain: The case of H. G., cited previously, and other examples in Fig. 2 provide many instances in which pain after infarction subsided as the cardiac work diminished. This raises the question of a casual relationship, such as is commonly believed to exist in simple angina of effort. It seems proper to suppose that cardiac work is a factor in the pain of infarction, but other factors must operate also. The disappearance of pain in some cases was not accompanied by any diminution of work that we could measure. Destruction of sensory nerves in the involved area, development of collateral circulation, and other processes of healing doubtless play a part in the relief of pain.

The work of the heart and the electrocardiogram: Since exercise will sometimes bring out electrocardiographic changes suggestive of coronary disease which are absent at rest, we sought for a correlation between the cardiac work and the changes in the electrocardiogram which took place during the subsidence of symptoms of infarction. We were unable, however, to demonstrate that any constant relationship existed.

Physiologic Considerations in Chronic Angina of Effort.—When our results are arranged according to the duration of the symptoms of coronary disease (Fig. 5), they give a viewpoint concerning the course of this disease. The general picture looks much like that of the closely related peripheral vascular diseases, i.e., a chronic course with a slow trend downward which may be hastened by acute vascular occlusions but also may be interrupted by periods of considerable recovery of function.

Our data also show that patients with angina may be divided into three main groups: Those with normal circulation, those with hypokinemia, and those whose pattern of cardiac ejection, as demonstrated by distorted ballistic form, is abnormal. We have examined our data

to discover whether or not these physiologic differences were accompanied by any variations in the clinical manifestations.

Cases of angina in which the circulation is normal: We have encountered two patients who have had angina pectoris for over five years whose cardiac work was normal when they were at rest, and, in one, both cardiac output and work were normal. The latter (W. T.), a man, 63 years of age, had had angina for 14 years, and remained employed as a guard all this time. In 1940, he developed very mild congestive failure, but recovered promptly on rest and digitalis. At present his heart is not enlarged as seen roentgenographically, his blood pressure is normal, and his electrocardiogram shows little abnormality. Certainly this patient has done very well.

The other patients with chronic angina whose circulations are well within the normal range, omitting those at the lower limit of normal, include a man, K. N., aged 33 years, who made an excellent recovery from a severe infarction about two years before; at present he is working hard and has no angina after any ordinary effort. Also in this group is D. B., a man, aged 60 years, who at the time of examination seemed to have completely recovered from the effects of a mild attack of infarction two years before, and, at present, three years later, is working hard and in good condition. Another with a normal circulation was M. F., a man, aged 65 years, who was still in the first year of his symptoms, and more incapacitated by nervousness than by angina. Finally, there was M. L., a woman with moderate hypertension in the fifth year of her symptoms, who came to the hospital for relief of a pain which was probably not cardiac in origin. Nevertheless, while in bed on the ward, she had an attack of substernal pain which was thought by the intern, who observed it, to be angina caused by excitement. If this is the correct interpretation, this is the only patient with angina and a normal circulation whose angina was not very mild.

Cases of angina in which there was marked hypokinemia: Fig. 5 shows data from fifteen patients whose circulation was -30 per cent or less. Nine of these had anginal attacks while in bed in the hospital. Four others developed congestive failure during the course of their disease. One, I. Z., who could walk only a city block without pain when this examination was made, has since grown worse, and her ballistocardiogram is now abnormal in form. The patient who seemed in best condition had cholelithiasis, and there was some doubt about the diagnosis of angina.

Cases of angina in which the ballistic forms were abnormal: Among these were found our most seriously ill patients. One died a week after the record was taken, and another within a few months. One patient's angina was so severe that paravertebral nerve block was performed to give relief. Another, who also had diabetes and hypertension, was having attacks of angina without exertion. Another, I. Z., whose

ballistic form became abnormal as her exercise tolerance diminished, has been mentioned. Still another, E. Q., has had angina for ten years, recently complicated by a uterine carcinoma.

Summary.—When the patient has a normal circulation the disease tends to be mild; patients with hypokinemia but normal ballistic form tend to be more incapacitated; and those with an abnormal ballistic form are by far the most seriously ill.

The Ballistocardiogram Compared With the Electrocardiogram.—We have been so often asked to compare these two methods of examination that a few words on this subject seem in order if we limit the discussion to our experience with coronary heart disease.

As anyone with knowledge of the fundamentals of these instruments would expect, they measure entirely different properties of the heart, and each can detect types of abnormality which escape the other. For example, in the first week after cardiac infarction the electrocardiographic abnormalities are at a maximum, whereas the ballistocardiograph reveals nothing abnormal in some cases. This situation is often reversed. Although they are not the only examples, the three patients with anginal-like attacks and also biliary tract disease, previously discussed, whose electrocardiogram showed little or nothing and whose ballistic records were profoundly abnormal, may be recalled.

Apparently the electrocardiogram most easily detects localized lesions when they are in a position to upset the balance of the electrical potential which is obtained by leading from the body surface. But, as is shown by the small and inconsistent changes which occur in the electrocardiogram after exercise, changes of function which affect the heart as a whole are not well detected. On the other hand, the ballistocardiogram, which is tremendously influenced by physiologic changes, such as exercise, will easily detect conditions affecting the heart as a whole, whereas the localized lesions, probably involving only a small fraction of the heart muscle, may not disturb function enough to influence records of resting subjects.

It must always be remembered, however, that the fact that the circulation is subnormal is not valid evidence that the heart is diseased. A major interest of workers with the ballistocardiograph is the study of the noncardiac types of circulatory abnormalities which are at present not detected by any other objective clinical method. Only when the form is abnormal does the ballistocardiogram give unqualified evidence that the heart itself is functioning abnormally, and abnormalities of form are found in only a small proportion of records of cardiac cases.

Clinicians must learn to view measurements of the amount of the circulation in much the way that they now regard estimates of blood pressure. One must not expect to diagnose the anatomic lesions found at autopsy, although the ballistic records may add to the evidence from which the presence of such lesions may be inferred. The function of the ballistocardiogram is to estimate how such lesions are affecting the ability of the heart to pump the blood and the result of treatment upon this function.

The Utility of the Ballistocardiogram in the Diagnosis of Coronary Heart Disease.—Some mention must be made of the utility of the ballistocardiogram in the diagnosis of coronary heart disease, for, although final conclusions are hardly warranted, tentative conclusions are. In the acute period immediately after infarction, the ballistocardiogram is too variable to give much support to this diagnosis. In the examination of patients with chronic coronary disease, it is much more valuable.

We have found only one case of chronic coronary heart disease in which the circulation was above the expected normal average; that patient, K. N., a young man, might be said to have almost completely recovered from a previous infarction. Thus, if the circulation is above the average normal, the chances of chronic coronary disease would seem to be remote.

In the diagnosis of angina pectoris, so much depends on the patient's statements that one is often misled by his failure to mention former illnesses or his misinterpretation of important symptoms. Additional evidence of an objective character is often very welcome. The ballistocardiogram provides this in the great majority of instances, either by disclosing an abnormal impact form, or by giving evidence of subnormal circulation. Other pathologic processes may cause similar ballistic changes, but these can usually be easily identified. A subnormal circulation in a patient over 50 years of age without obvious signs of organic heart disease, cardiac arrhythmia, congestive failure, endocrine disease, or hypertension, who is not convalescent, moribund, or in shock, should lead one to suspect coronary heart disease. The patients with essential hypokinemia or neurocirculatory asthenia, who also have a subnormal circulation without any other abnormalities that are demonstrable by the clinical methods in ordinary use, are usually younger persons.

Besides giving aid in diagnosis, the ballistocardiograph permits calculation of the cardiac work, and therefore the measurement of its strength or weakness by a method more direct than the usual clinical techniques. Weakness of the heart may manifest itself in more than one way. In one type the work per minute diminishes; in another it is maintained, but only by drawing on the cardiac reserve. In previous investigations^{11, 12} we studied both the size of the heart and its work; cardiac enlargement out of proportion to performance per beat was found to be characteristic of patients who had had, or were threatened with, congestive failure. In these the work per minute was often normal. In coronary heart disease the weakness was not of this type, an observation that we have confirmed in this investigation, for we have roentgenologic evidence of the size of the heart in the great majority of our cases. As is well known, cardiac hypertrophy and dilatation are not characteristic of such cases; perhaps the widespread coronary damage prevents the employment of these reserves. In a majority of the cases of coronary disease, the weakness is manifested by a reduction

of the basal work per minute. Our evidence suggests that the extent of this abnormality is a measure of the severity of the disease.

SUMMARY

Ballistocardiograms were made 106 times on 55 patients with coronary heart disease.

In the acute period after infarction the circulation may be either normal or below. If normal, it tends to diminish, and usually reaches a minimum below the normal limit between the third and fifth week. Later, recovery sets in. The left ventricular work, as calculated from the cardiac output and the blood pressure, follows a generally similar course.

In chronic coronary heart disease, with angina of effort, the circulation is subnormal in the great majority of cases, and the ballistocardiogram provides objective evidence to support the diagnosis.

Abnormalities of the form of the ballistocardiogram are frequently encountered in coronary heart disease, usually when the patient has greatly reduced exercise tolerance.

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THE ANATOMIC CAUSE OF ELECTROCARDIOGRAPHIC CHANGES IN VIRUS MYOCARDITIS OF RABBITS

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FOR many years there has been a clinical concept of the debility of the cardiovascular system resulting from or accompanying a number of acute infectious diseases. Of these, perhaps diphtheria, influenza, and scarlet fever are followed most commonly by instability of the circulatory system that is evidenced mainly by subjective symptoms, but occasionally by abnormalities of heart rate or blood pressure and transient alterations in the electrocardiogram.¹⁻³ For these there has never been any well demonstrated anatomic cause. A variety of other diseases, chief among which are many of the virus infections of man, are also said to be accompanied by myocarditis. Measles, mumps, smallpox, yellow fever, psittacosis, certain pneumonias, and acute infections of the upper respiratory tract have been implicated.¹ In most instances the evaluation of the disturbed cardiac condition rests solely on clinical and electrocardiographic observations, but even in those cases in which necropsy is done there is seldom the possibility of correlating the electrocardiograms with the inflammatory lesion in the myocardium.

This situation has resulted in two points of view. On the one hand there is the opinion that the subjective symptoms of cardiovascular incompetence and the transient deviation of the electrocardiogram from the normal pattern are the result of some toxic influence which alters the dynamics of the heart without causing any morphologic change, whereas, on the other hand, there is the more conservative opinion that true inflammatory lesions exist in the myocardium of the abnormally functioning heart.

In rheumatic fever, also, although the cause of this disease remains obscure, the cardiac involvement which occurs in the early and acute stages is often manifested, among other ways, by changes in the electrocardiogram. The correlation of these changes with morphologic alterations in the heart is almost invariably precluded by the recovery of the patient, or at least by his continued survival and the evolution of the acute lesion into the so-called "chronic rheumatic heart."

A method of elucidating these obscure states and the possibility of explaining them by visible anatomic alterations, if only by analogy, has recently arisen in the demonstration of the various cardiac lesions which occur in rabbits during the course of virus infections. It has been shown^{4, 5} that rabbits inoculated subcutaneously or intratesticularly with a variety of filtrable viruses develop cardiac lesions which,

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when the animal has been subjected to suitable preparatory procedures, are severe and extensive. The lesion is predominantly a myocarditis, regardless of the nature of the infecting virus.

The present paper consists of an electrocardiographic study of some of these experimentally induced virus infections, both in the initial stage of the acute infection and in the stages of recovery, made in an attempt to show that the abnormality in the electrocardiogram is dependent upon structural changes and visible lesions in the heart.

METHOD

Virus myxomatosum, pseudorabies virus, vaccine virus, virus III, and Shope's tumor strain and Andrewes' inflammatory strain of the fibroma virus may produce a specific myocarditis in rabbits when inoculated peripherally.⁵ The frequency and severity of the myocarditis are markedly increased if the animal is subjected to some procedure which is designed to produce a transitory alteration in the dynamics of the circulation. Since the simplest and most successful of these procedures is the intravenous injection of approximately 50 c.c. of 20 per cent gum acacia solution immediately before the intratesticular inoculation of the virus, this method was used in the present investigation to produce the cardiac lesions.

Virus III^{6, 7} and Andrewes' inflammatory strain of the fibroma virus^{8, 9} were the infecting agents of choice because neither of these viruses is sufficiently virulent to kill; yet infection with each results in a high incidence of cardiac involvement.

TABLE I

CORRELATION OF ACUTENESS OF INFECTION,* ELECTROCARDIOGRAPHIC ABNORMALITIES, AND MYOCARDITIS IN RABBITS INOCULATED WITH VIRUS III

RABBIT NUMBER	TIME OF ELECTRO-CARDIOGRAM†	FEVER AND ORCHITIS	ELECTROCARDIOGRAPHIC ABNORMALITIES	MYOCARDITIS
1	2-9	Present	Marked	Marked
2	2-9	Present	Slight	Moderate
3	2-9	Present	Absent	Marked
4	2-9	Present	Absent	Moderate
5	3-13	Present	Marked	Moderate
6	3-13	Present	Marked	Moderate
7	3-13	Present	Marked	Marked
8	3-13	Present	Absent	Marked
9	14	Present	Moderate	Moderate
10	14	Present	Moderate	Absent
11	14	Present	Absent	Absent
12	14	Present	Absent	Absent
13	14	Absent	Absent	Absent
14	14	Absent	Absent	Absent
15	14	Absent	Absent	Absent
16	14	Absent	Absent	Absent
17	14	Absent	Absent	Slight
18	14	Absent	Absent	Slight
19	14	Absent	Absent	Slight
20	20	Absent	Absent	Absent
21	20	Absent	Absent	Absent
22	20	Absent	Absent	Slight
23	24	Absent	Absent	Slight
24	24	Absent	Absent	Slight
25	24-26	Absent	Marked	Marked

*Acuteness of infection was judged by the presence of fever and orchitis, recognizable in the living animal. It is the presence or absence of these signs at the time of obtaining the electrocardiogram which is tabulated.

†The numerals indicate the number of days after inoculation at which the electrocardiogram was obtained. Two numerals separated by a hyphen indicate that serial records were made during that period.

All of the rabbits were young males weighing between 1,500 and 2,500 grams. They were not selected as to breed or strain and were acquired from several sources.

Approximately 50 c.c. of 20 per cent gum acacia solution in distilled water or physiologic saline were injected into the marginal ear vein of each of 46 rabbits. Immediately thereafter 25 of these rabbits were inoculated in each testis with 0.5 c.c. of a 5 per cent suspension of virus III infected testis and 21 were similarly inoculated with 0.5 c.c. of a 5 per cent suspension of inflammatory fibroma infected testis. The suspensions which were used for inoculation were prepared by grinding an infected testis, excised during the acute stage of the disease, under sterile conditions, with sand and a small amount of 0.85 per cent salt solution in a mortar. The resultant paste was then diluted to 5 per cent with additional salt solution.

In all of the experimental animals, successful infection was evidenced by an elevation of temperature and obvious enlargement and induration of the inoculated testis.

The method of obtaining electrocardiograms has been described in detail in a preceding publication.¹⁰ It consisted of using the three conventional limb leads, and, in addition, a left chest and a right chest lead. Tracings were made daily or on alternate days on 15 rabbits in the virus III infected group and on 7 rabbits in the fibroma infected groups during the stage of the acute infection, which was considered to be the period from 2 days after inoculation through the ensuing 9 to 14 days. Electrocardiograms were taken on the remaining 10 rabbits in the virus III group at intervals of 14, 20, or 24 days after inoculation, and, on the remaining 14 rabbits in the fibroma group, 14, 24, 31, and 37 days after inoculation (Tables I and II).

TABLE II

CORRELATION OF ACUTENESS OF INFECTION,* ELECTROCARDIOGRAPHIC ABNORMALITIES, AND MYOCARDITIS IN RABBITS INOCULATED WITH THE INFLAMMATORY FIBROMA VIRUS

RABBIT NUMBER	TIME OF ELECTRO- CARDIOGRAM†	FEVER AND ORCHITIS	ELECTRO- CARDIOGRAPHIC ABNORMALITIES	MYOCARDITIS
1	3-10	Present	Absent	Marked
2	3-10	Present	Absent	Moderate
3	3-10	Present	Absent	Absent
4	4-14	Present	Absent	Marked
5	4-14	Present	Absent	Slight
6	4-14	Present	Absent	Slight
7	4-14	Present	Absent	Absent
8	14	Absent	Absent	Absent
9	14	Absent	Absent	Slight
10	14	Absent	Absent	Slight
11	24	Absent	Absent	Slight
12	24	Absent	Absent	Moderate
13	24	Absent	Absent	Marked
14	24	Absent	Absent	Absent
15	31	Absent	Absent	Slight
16	31	Absent	Absent	Slight
17	37	Absent	Absent	Slight
18	37	Absent	Absent	Slight
19	37	Absent	Absent	Slight
20	37	Absent	Absent	Slight
21	37	Absent	Absent	Absent

*See footnotes to Table I.

Tracings taken on 9 of the virus III infected rabbits before the induction of the disease, together with the previously published series of electrocardiograms¹⁰ on normal rabbits, served as controls. Any possibility of an effect on the electrocardiogram brought about by the large intravenous injection of acacia alone was precluded by the fact that many of the experimental animals which had received acacia, as well as virus, showed no abnormality in the electrocardiogram. The

absence of effect of acacia alone was further confirmed in 3 rabbits by tracings taken both during the injection and at 2- to 6-day intervals thereafter.

The rabbits in both groups which were studied electrocardiographically during the early and acute stages of the disease were killed on the day the last tracing was made in order to have close correlation between the anatomic condition of the heart and the evidence of its functional state. Those animals which were studied at a later period, when all clinical manifestations of infection had subsided, were frequently not killed until several days after the last tracing had been made. It seemed probable that, after the long interval following inoculation, any cardiac lesions which might have persisted would be in the nature of a fibrous scar which could change but little.

The hearts were fixed intact in Zenker's solution and then trimmed by longitudinal section into blocks, which included all four chambers and valves. This method, described in detail in a previous paper,⁴ makes possible the histologic study of all parts of the heart in their normal relationship.

RESULTS

In the normal rabbit electrocardiogram¹⁰ there are marked spontaneous changes in the form, voltage, and direction of some of its components. Transient reversal of the T wave in Leads I or III and in the chest leads is frequently observed. T₂, however, is constantly upright, so that inversion of T₂ can be used as a criterion of significant abnormality. Slight RS-T segment deviations, never exceeding one millimeter, are frequently encountered. The P-R interval never exceeds 0.10 sec., and the duration of the QRS complex never exceeds 0.04 second. Abnormal rhythms are not seen in the normal animal. Hence prolongation of the P-R interval beyond 0.10 second and the inception of abnormal rhythms can likewise be regarded as criteria of significant dysfunction.

The results of the experiments with virus III are shown in Table I. It is evident at once that significant changes in the electrocardiogram occur, as a rule, only when a marked anatomic alteration is present in the myocardium, but that both minor and severe lesions may exist without bringing about any noteworthy alteration in the tracing. Rabbits 1 to 8, which were inoculated with active virus, developed well-marked and widespread necrotizing and inflammatory cardiac lesions, as well as definite clinical evidence of disease. Five of these 8 animals also had significant alterations in their electrocardiograms. The most serious of these was transient, complete auriculoventricular heart block (Fig. 1, rabbit 7), or transient RS-T segment deviation of more than one millimeter.

The photomicrographs (Figs. 2 and 3) of the heart of the animal (rabbit 7) on which such tracings were obtained illustrate the type of lesion in the myocardium. The morphology and localization of these cardiac lesions have been described in considerable detail in a previous publication.⁴ In brief, they consist of local or diffuse areas of necrosis and disappearance of muscle fibers, accompanied by an infiltration of large mononuclear leucocytes, lymphocytes, and occasional polymorphonuclear leucocytes. There is a variable amount of fibrous tissue re-

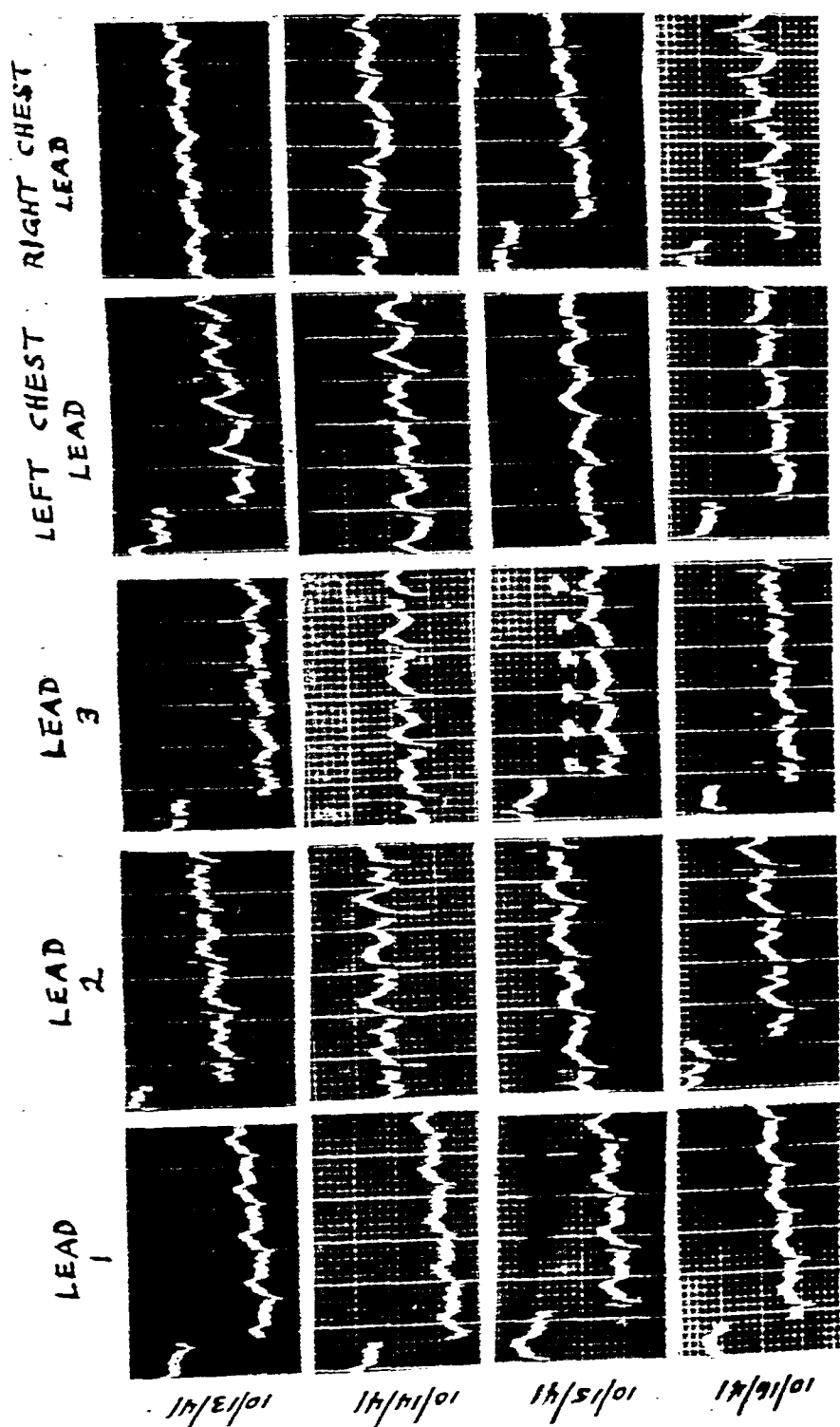


FIG. 1. (See continuation and legend on opposite page.)

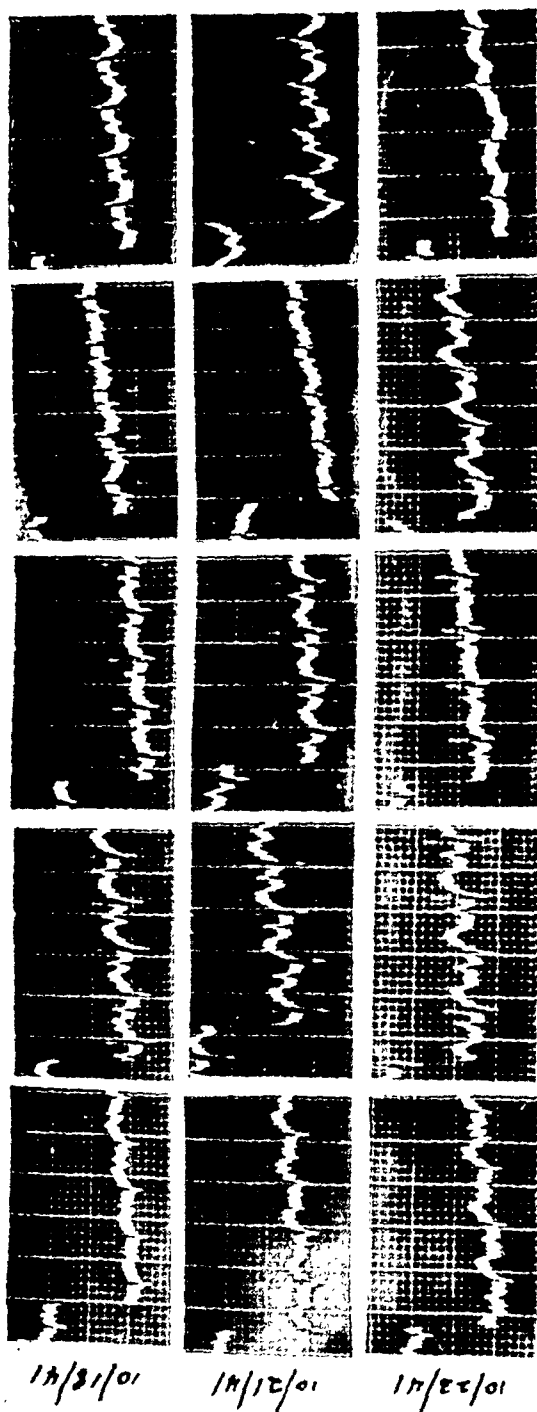


Fig. 1.—Sequential five-lead electrocardiogram taken from rabbit 7 during the acute stage of experimental virus III infection. The tracings, taken 4 days (10/14/41) and 5 days (10/15/41) after inoculation, show bizarre complexes which, on careful caliper examination, are found to be characteristic of complete auriculoventricular heart block. On the following day (10/16/41) there is a return to normal sinus rhythm. The transient T-wave reversal in the left chest lead is not significant, for it may occur in the normal rabbit.

placement. Intranuclear inclusion bodies which are typical of the virus may be found in the mononuclear cells, the fibroblasts, or the muscle cells.

It is noteworthy, however, that severe myocarditis may be present, as in rabbits 3 and 8, without any electrocardiographic evidence thereof.

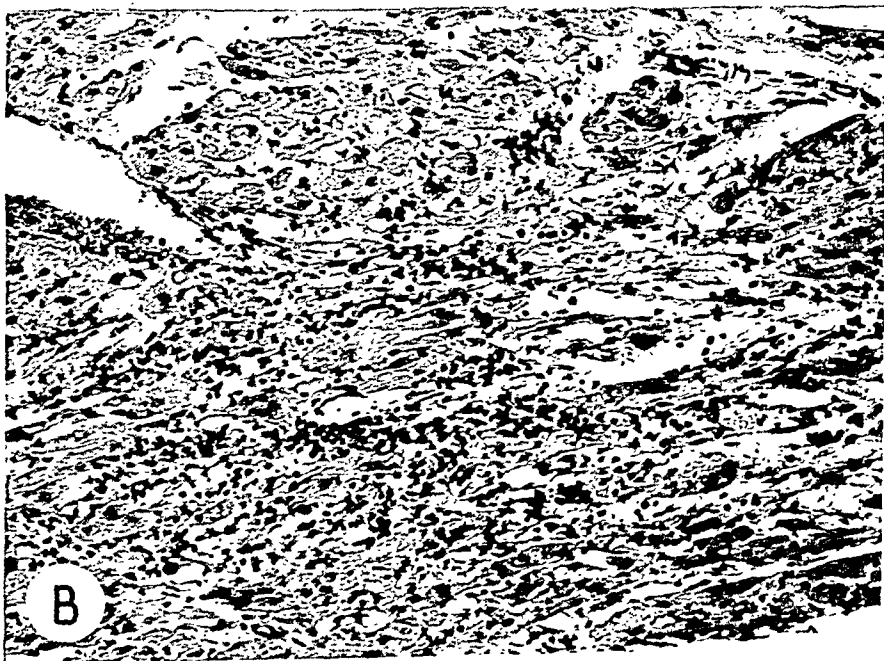


Fig. 2.—Sections of the myocardium of rabbit 7, killed 13 days after inoculation. A. Collection of leucocytes in the myocardium between and replacing muscle fibers. The exudate is concentrated at the margin of an arteriole. Hematoxylin and eosin, $\times 150$. B. Diffuse leucocytic infiltration and myocardial necrosis. Hematoxylin and eosin, $\times 150$.

Rabbits 9 to 15 were inoculated with virus which was presumably attenuated. Three of these animals failed to develop any clinically recognizable disease, and only one had myocardial lesions. In this latter rabbit, 9, and in one other, 10, the electrocardiograms were beyond the limits of normal variation.

Rabbits 16 to 25 were studied 14 to 24 days after the initial inoculation of virus which was known to be active. In none was there any

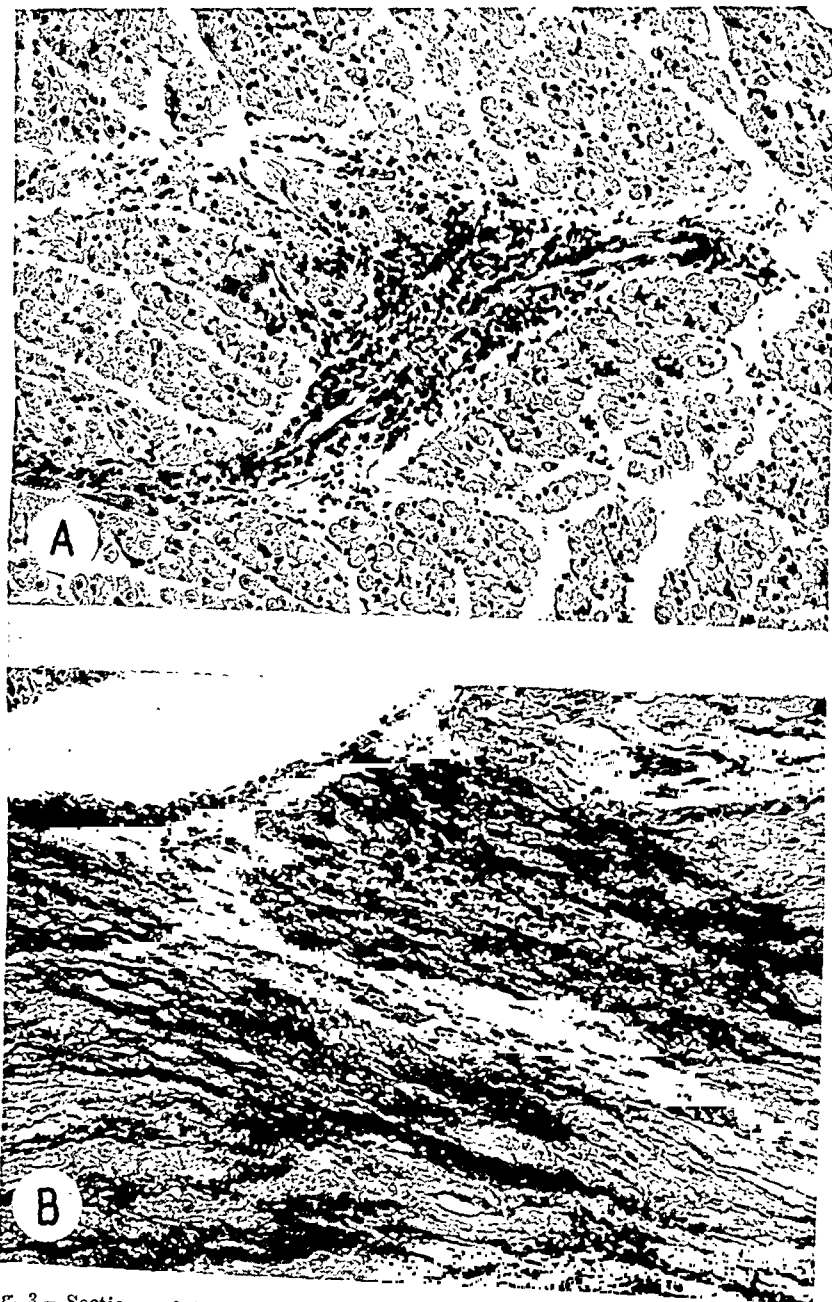


Fig. 3.—Sections of the myocardium of rabbit 7, killed 13 days after inoculation. A. Localized perivascular infiltration. Hematoxylin and eosin, $\times 150$. B. Infiltration, necrosis, and fibrous tissue replacement in Purkinje's fibers of the right ventricle. Masson's trichrome stain, $\times 150$.

clinical evidence of persisting infection. The majority of the hearts contained the small scars and focal collections of lymphocytes that are characteristic of a previous myocarditis, but in one, 25, the myocardial fibrosis and lymphocytic infiltration were extreme. This rabbit, 25, was the only one of the entire group in which the electrocardiogram was abnormal. When the record was first obtained, 24 days after inoculation, it showed paroxysmal auricular tachycardia with partial heart block (P-R interval, 0.12 second). Two days later normal rhythm had returned.

As shown in Table II, infection with the fibroma virus failed to bring about significant alteration in the electrocardiogram, even in those animals whose hearts contained lesions which could be demonstrated anatomically to be extensive.

DISCUSSION

The outstanding observation which can be made from the results of these experiments is the definite association of electrocardiographic abnormality with anatomic alteration. In other words, a morphologic cause of abnormal function is again demonstrated. In these infections of the rabbit, at least, the concept of toxicity, i.e., of some hypothetically intrinsic pharmacologic action of disease on the heart, as the cause of the abnormality of the electrocardiogram becomes unsatisfactory and untenable. With one exception, a significant variation from the normal rabbit electrocardiogram never occurred in the absence of histologically demonstrable myocarditis. This one exception, however, is not disturbing because it is easily conceivable that a small but locally severe lesion might occur in some part of the cardiac conduction system and yet be missed in the comparatively gross anatomic examination. Rather, it is surprising that there were not more animals with minute but significantly placed lesions which escaped observation but, nevertheless, changed the pattern of the electrocardiogram.

The value of the electrocardiogram in this type of disease is well shown by the fact that in the series of twenty-five animals there were only three in which the anatomic lesion in the heart was more than slight on which the diagnosis could not have been made by the abnormality of the tracing. This number represents a positive diagnostic accuracy of 88 per cent, a figure which compares well with other indirect methods of clinical examination. If the one rabbit (10) in which an electrocardiographic abnormality was encountered in the absence of a demonstrable lesion is included, the total diagnostic accuracy remains at the high figure of 84 per cent.

It is at first glance surprising that the animals inoculated with the inflammatory fibroma virus failed to develop any demonstrable irregularity in cardiac function. Reference to Table II, however, shows that even in those rabbits which were studied during the acute stage of the disease, when fever and orchitis existed, the myocarditis was marked in only two instances. With this virus in the present series of experiments, the lesion in the heart was more often an interstitial

proliferation of fibrous tissue, with little of the acute, inflammatory, exudative, and necrotizing reaction. The former type of reaction spares the structure of the muscle fibers, especially the conducting mechanism, so that no electrocardiographic abnormality may be expected. If this explanation is true, and since these animals were studied during the acute febrile period of their disease, the theory of toxicity as the cause of cardiac dysfunction again breaks down.

SUMMARY

Electrocardiographic studies were made on 25 rabbits which had been inoculated intratesticularly with virus III. During the acute stage of the resulting disease, the majority of these animals developed a histologically demonstrable myocarditis, and, after recovery from the infection, small scars were found in the myocardiums of many. Definite abnormalities in cardiac function, including complete auriculoventricular heart block, were demonstrated in the electrocardiogram during the period in which the acute myocarditis existed. The electrocardiogram failed to show the presence of a noteworthy myocarditis in only 3 animals, and in only one instance was it impossible to demonstrate myocarditis when the tracing was significantly altered. The electrocardiographic diagnosis was thus accurate in 84 per cent of the cases. This association of the abnormal electrocardiogram with the structural lesion in the heart leads to the conclusion that, in this disease of the rabbit, disturbed function is caused by actual lesions, and not by the toxicity of the disease.

Twenty-one rabbits which were inoculated intratesticularly with Andrewes' inflammatory strain of the Shope fibroma virus were studied similarly. Although in the hearts of a few of these animals interstitial myocardial fibrosis occurred, the muscle cells escaped for the most part, and in no animal was any abnormality in the electrocardiogram demonstrated.

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Clinical Reports

REPORT OF A CASE OF COR BILOCULARE WITH PERSISTENT TRUNCUS ARTERIOSUS

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COR biloculare with persistent truncus arteriosus was first described by Preisz,¹ in 1890. However, it was first fully described and studied by Abbott;² and in her series of 1000 cases of congenital cardiac disease it occurred nine times. The average duration of life in this series was three and three-fourths years. The patient who lived the longest attained the age of thirty-six, and was reported by Carr, Goodale, and Rockwell,³ in 1935. The latter case of cor biloculare with persistent truncus arteriosus was similar in several respects to the present one and occurred in a male who, during his entire life, had a low cardiac reserve and was not cyanotic until a single period of strenuous exertion. Cyanosis then developed and gradually increased, and he died with congestive failure. The heart in this case was hypertrophied, and there was a single, large arterial channel arising from the right ventricle which was guarded by a semilunar valve with two cusps. The pulmonary arteries were exceptionally large and arose just above the valve. Directly beneath the arterial ring and valve there was a large interventricular septal defect.

Benjamin, Landt, and Zeek⁴ reported a case of what was functionally a biloculate heart with a single arterial channel. Their patient, however, had an atretic right ventricle and pulmonary artery which, they believed, did not function. However, their specimen was incomplete in that the ductus arteriosus was not available for examination.

During the fourth week of intrauterine life a small ridge develops on the anterolateral surface of the common ventricle. At the same time a similar ridge develops in the truncus arteriosus, with four bulges at the base of this vessel. The bulbar septum divides one of these bulges, so that there are three to each trunk which become aortic and pulmonary valves. The ventricular septum and bulbar septum then fuse.

The present case is presented not only because of the rarity of this anomaly, but because of the apparently unusual fact that cyanosis occurred only shortly before death. The single arterial channel in this case had three well-developed semilunar cusps, and, according to some of the earlier authors, this would not be a true case of cor biloculare with persistent truncus arteriosus. However, according to Abbott,

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several well-authenticated cases with three cusps or even less have been reported.

CLINICAL RÉSUMÉ

The patient was a three-day-old white male, born in the San Francisco County Hospital. He was delivered by internal podalic version and extraction, and at the time of birth weighed 6 pounds, 3½ ounces. The infant breathed spontaneously; the color was described as good, and it was not cyanotic. No abnormalities were noted at the time of delivery. On the second day after delivery, the baby was transferred to the Isolation Department because of a small impetiginous lesion on the upper lip. Physical examination at that time by the pediatric resident revealed a small, newborn infant who was crying lustily and appeared quite healthy.

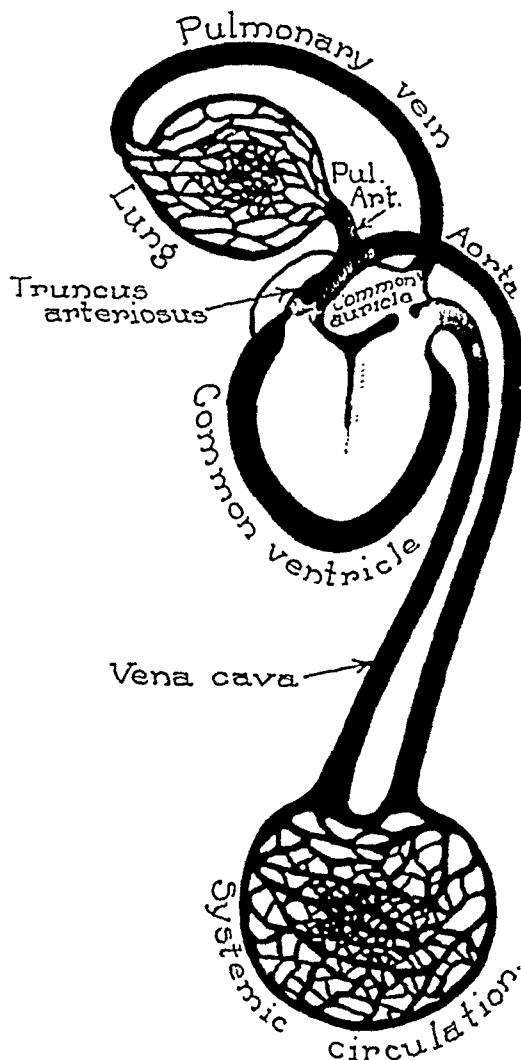


Fig. 1.—Diagram of greater and lesser circulation.

The baby had a definite subicteric tinge. The lungs were normal to percussion and auscultation. The heart was regular, and the sounds were of good quality. No murmurs were heard. The liver was palpable at the level of the umbilicus below the right costal margin. Later, on the second day after delivery, the extremities were noted to be slightly cyanotic, and, on the morning of the third day, the infant became extremely cyanotic, breathed with great rapidity and difficulty, and died suddenly.

AUTOPSY OBSERVATIONS

The autopsy was performed at the Coroner's Office of the City and County of San Francisco by the author. The body was that of a small male infant which weighed slightly less than six pounds and showed no external abnormalities. The lungs were only partially aerated, with numerous areas of collapse and edema.

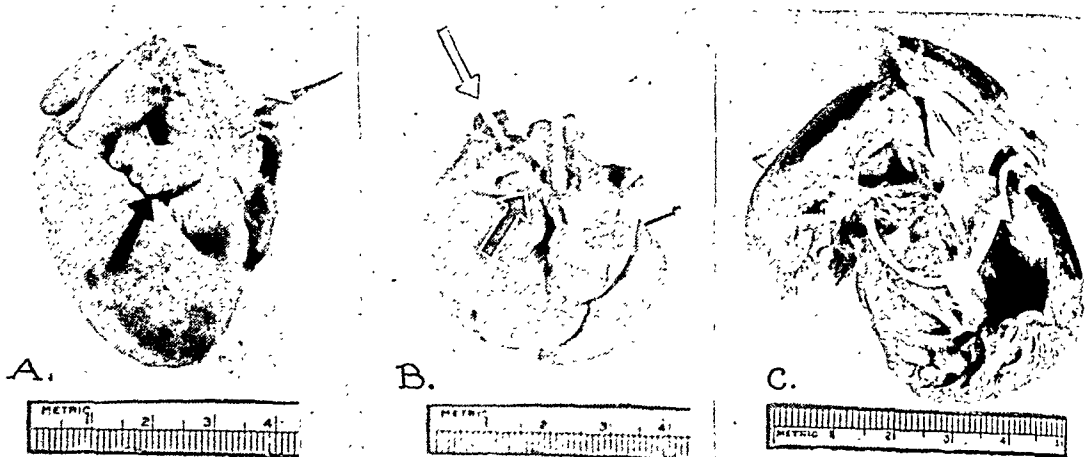


Fig. 2.—A. Anterior view of heart, black arrow indicating incompletely developed, nonfunctioning left auricle. White arrow and white line indicate direction of systemic blood flow.

B. Superior view, showing enlarged common auricle with truncus arteriosus and pulmonary artery. White arrow indicates direction of blood flow; black arrow indicates pulmonary veins.

C. The heart opened up, showing the direction of blood flow and the semilunar valves at the base of the truncus arteriosus.

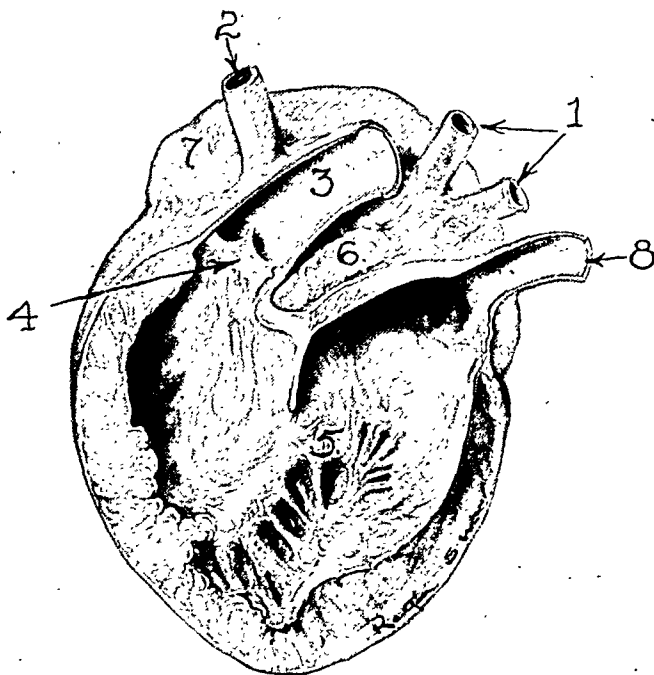


Fig. 3.—Drawing: 1. Pulmonary veins. 2. Pulmonary artery. 3. Truncus arteriosus. 4. Semilunar valves. 5. Common ventricle. 6. Nonfunctioning, incompletely developed left auricle. 7. Common auricle. 8. Vena cava.

The pulmonary arterial vessels were heavily congested. The heart was found to be enveloped in a normal pericardium and was not enlarged. It measured $3.5 \times 3.0 \times 5.0$ cm. There were a single, large ventricular chamber and a single auricle. The vena cava emptied into the base of the auricle posteriorly on the right side. Slightly higher up, two small pulmonary veins also drained into the auricle. The functioning auricle lay on the right side, was smooth, and projected around the right side of the base of the heart like a large finger. A smaller appendage, with no lumen, was found projecting around the left side of the base of the heart. Near the opening of the functioning right ventricle a single, veil-like structure was attached to the ventricular wall by a poorly developed chorda tendineae. This resembled an incompletely developed atrioventricular valve or an incompletely developed membranous septum. Projecting from the right side of the common ventricle was a single, larger arterial channel, at the base of which was a semilunar valve composed of three well-developed cusps. Well above this valve was a single vessel which again divided and entered the pulmonary parenchyma on either side. The main vessel then continued on as the arch of the aorta, with its branches. The remaining portions of the aorta in the thorax and abdomen were not remarkable. The venous return from the lungs, as previously mentioned, was through two small veins which entered near the vena cava at the base of the functioning right auricle, or common auricle.

The remainder of the autopsy was not remarkable except for slight enlargement and congestion of the liver and spleen.

SUMMARY

A case of cor biloculare with persistent truncus arteriosus in a three-day-old infant, with the unusual feature that cyanosis occurred only shortly before death, is presented.

The blood flow through the lesser circulation was markedly increased at the time of birth, so that the systemic blood was well aerated or oxygenated, at least to the subcyanotic level; death was caused by diversion of some of the blood from the lesser to the greater circulation, thereby lessening the total output of oxygenated blood.

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ISOLATED DEXTROCARDIA, WITH DIODRAST STUDIES

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AND GEORGE P. ROBB, M.D.
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INTRODUCTION

EVERYONE is familiar with the mirror-image dextrocardia which almost invariably is associated with transposition of all the viscera. The rare cases of isolated dextrocardia are subject to associated cardiovascular anomalies and require individual study. In the case herein reported, visualization of the cardiac chambers by the diodrast method of Robb and Steinberg¹⁵ was of great aid in understanding the pathologic anatomy. So far as we have been able to learn, this is the first study of its kind.

CASE REPORT

History.—B. I., a 55-year-old Italian housewife, was first admitted to Grasslands Hospital June 10, 1940. Beginning at the age of 35, or earlier, she had had attacks of "palpitation." These were usually accompanied by dyspnea and cyanosis, sometimes by vomiting and teichopsia, and once by hemoptysis. Dr. J. A. Costa, in referring her to the hospital, mentioned attacks of paroxysmal tachycardia which occasionally lasted several days and resulted in pulmonary edema, requiring oxygen therapy and full digitalization. Between attacks, which were diminished in frequency by the administration of one cat unit of digitalis daily, she felt perfectly well. In the week before admission she suffered two mild nocturnal attacks.

The family history and past history were essentially negative. Seven pregnancies were apparently well tolerated.

Physical Examination.—The patient was 59½ inches in height and weighed 125 pounds. She was lying comfortably in bed, without dyspnea or cyanosis. The point of maximum intensity of the heartbeat was felt in the right fifth intercostal space. The right border of the heart was percussed 11 cm. to the right of the midsternal line in the fifth intercostal space and 6 cm. in the third intercostal space. The left border was percussed 2 cm. to the left of the midsternal line in the fourth left intercostal space. The heart sounds were loud; the second sound at the base was louder to the right than to the left of the sternum. A loud systolic murmur and a faint, high-pitched, blowing diastolic murmur were present and were heard best in the right third intercostal space. The systolic murmur was widely transmitted over the entire precordium. No thrill was palpable. The blood pressure was 125/80 in both arms and 140/80 in the legs. The pulsation of the abdominal aorta was felt to the left of the vertebral column. The edge of the spleen was felt just under the left costal margin, and the liver descended, on inspiration, 4 cm. below the right costal margin.

Laboratory Examinations.—The Kline exclusion test was negative. The blood cell counts, the urine, the blood sugar, and the nonprotein nitrogen were normal. Between attacks the circulation times were: ether, 8 seconds, sodium cyanide, 13 seconds; paraldehyde, 9 seconds, and calcium gluconate, 12 seconds; the venous pressure was 10 cm. of water.

From the Medical Service of Dr. M. deTouart, Grasslands Hospital, Valhalla, N. Y.
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Roentgenographic Examinations.—The teleoroentgenograms of the chest showed that the heart was enlarged, and that it was in the right thoracic cavity, with considerable bulging of the right supraventricular shadow. The aortic knob was on the left. Fluoroscopic examination revealed increased pulsations of the right lower (ventricular) and supraventricular shadows. The aortic arch passed over the left main bronchus and descended on the left side of the spine. The aortic pulsations appeared to be normal. There was no "hilar dance."

An esophagram showed the usual left aortic arch impression upon the esophagus. The stomach was on the left, in the position in which it is found in normal persons (Fig. 1).



Fig. 1.

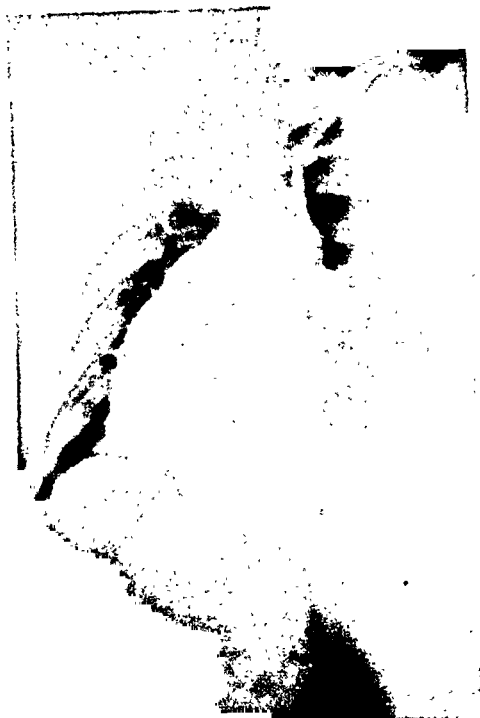


Fig. 2.

Fig. 1.—The heart occupies the right thoracic cavity. There is the usual left aortic arch impression upon the esophagus, and the stomach is on the left.

Fig. 2.—Roentgenogram taken two and one-half seconds after the injection of 50 c.c. of 70 per cent diodrast reveals a left-sided superior vena cava coursing downward and then to the right above the diaphragm to empty into the right auricle. The venous auricle and ventricle are seen on the right. The outflow tract of the venous ventricle forms a prominent conus on the right.

Roentgenograms were taken after the intravenous injection of 50 c.c. of 70 per cent diodrast, with the aid of Dr. Robb, according to the technique of Robb and Steinberg.¹⁵ They showed that the venous auricle and ventricle were on the right side, with a left-sided superior vena cava coursing downward and then to the right above the diaphragm to empty into the right auricle (Fig. 2). The outflow tract of the right ventricle formed a prominent pulmonary conus. The left side of the posteroanterior roentgenogram (taken 10 seconds after the injection) was found to consist of the left ventricle and aorta (Fig. 3).

Electrocardiograms.—The first electrocardiogram (taken before admission) showed depressed S-T segments and diphasic T waves in all leads, with regular sinus rhythm and occasional premature ventricular contractions. A digitalis effect was evident. The electrocardiogram reproduced herewith (Fig. 4) is typical of those between attacks, when there was no digitalis or quinidine effect. It shows slurring

of the QRS in all leads, slightly depressed S-T segments in Leads I and II, a slightly elevated S-T segment in Lead IV F, an inverted T wave in Lead I and a QRS of 0.10 seconds. The next tracing (Fig. 5) reveals paroxysmal supraventricular tachycardia, with abrupt cessation on carotid pressure.



Fig. 3.—Roentgenogram taken ten seconds after the injection of 50 c.c. of 70 per cent diodrast shows the arterial ventricle and aorta forming the left side of the heart. The right side of the diaphragm is slightly lower than the left.

Course.—A mild attack of paroxysmal tachycardia was easily stopped by carotid pressure. An attack in July, 1940, was similarly controlled. The patient was readmitted July 20, 1940. She was dyspneic because of a five-day-old attack which had continued despite quinidine and vagal stimulation. It was again stopped by carotid pressure (Fig. 5). She was given 3 grains of quinidine four times a day, and $\frac{1}{30}$ grain of strychnine three times a day after a second attack. On September 13, 1940, one week after stopping the above drugs, the patient was readmitted in another attack of paroxysmal tachycardia. She was dyspneic, orthopneic, and cyanotic, and had hypotension and generalized moist râles. The usual treatment for pulmonary edema was administered. Quinidine was given by mouth in a dose of three grains every three hours. The attack stopped after thirty grains had been administered. Previous to that, vagal stimulation, emetics, acetyl-beta-methylcholine, and quinidine intravenously had been ineffectual. Quinidine and strychnine were then continued in maintenance doses, and these kept her free from attacks for six months.

COMMENT

The following terms should be clarified. According to Lichtman,⁷ "Dextrocardia" includes "... cases in which the heart, in its own de-

velopment independent of disease and anomaly in surrounding structures, assumes a position in the right side of the thorax with the apex pointing to the right." "Dextroversio cordis" includes "... cases in which the displacement of the heart is dependent on a congenital or acquired extrinsic cause." By "isolated dextrocardia" is meant "heterotaxia of the heart alone with normal position of all other viscera."

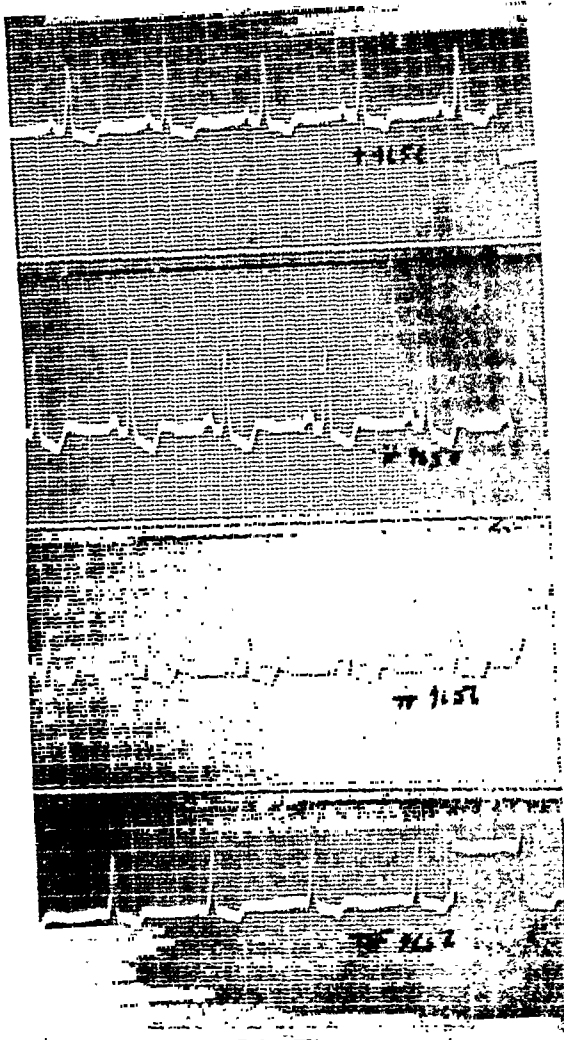


Fig. 4.—Electrocardiogram taken between attacks of paroxysmal tachycardia, when there was no digitalis or quinidine effect. Lead I shows the upright P and QRS, with the inverted T, which is fairly typical of isolated dextrocardia without "mirror-image."

Less than 200 cases of isolated dextrocardia have been reported. The case presented here is an example of the usual type of isolated dextrocardia, that is, without "mirror-image" inversion of the heart chambers. "Mirror-image" inversion always exists in situs inversus totalis, but rarely with isolated dextrocardia. In contradistinction to situs inversus totalis and isolated "mirror-image" dextrocardia, cases of isolated dextrocardia similar to the one herein reported are subject to other

cardiovascular anomalies. Lichtman⁷ lists only three authentic cases of isolated dextrocardia without other cardiovascular anomalies. Although the life expectancy of patients with "isolated" dextrocardia (Roesler) is fourteen years, those who survive to the age of twenty may have a life expectancy of forty-four years. Symptoms and signs of congenital heart disease are usually evident in infancy in these cases, and death frequently occurs within the first year. Our patient is thus very unusual, if not unique, in having survived to the age of fifty-five. Certainly her seven pregnancies are rather remarkable. It is also noteworthy that none of her children has a demonstrable cardiac defect.

In a case reported in 1915, by Moffatt and Neuhof,¹¹ of isolated dextrocardia with many congenital cardiac anomalies and death at the age of three and one-half years, there were short runs of paroxysmal auricular tachycardia.

Few other arrhythmias associated with dextrocardia are reported in the literature. In Lichtman's second case of isolated dextrocardia⁷ and Lloyd's⁸ case of situs inversus totalis auricular fibrillation was present. In other cases, associated with acquired mitral stenosis, such as Krestin's,⁵ there was the same arrhythmia. Abnormalities of the conduction mechanism have occurred rarely.^{5, 10, 13} The arrhythmias in these cases have usually accompanied multiple cardiac defects, with enlargement of the heart and myocardial damage, as in our case.

The diodrast studies in our case clearly demonstrated the relationship of the heart chambers and the left-sided aortic arch (both of which are usual in isolated dextrocardia).^{10, 16} Proof in the past has not been possible without post-mortem examination. From the diodrast and fluoroscopic studies we may conclude that the aorta was to the left of, and probably anterior to, the pulmonary artery, i.e., that these were transposed. In the terminology of Spitzer, 90° detorsion had taken place. The anomalous course and termination of the superior vena cava (we have not disproved the presence of a right-sided one as well) were also interestingly shown (Fig. 2).

It should be noted that the right side of the diaphragm was lower than the left, despite the presence of the liver on the right side. This is consistent with the theory¹⁶ that the height of the diaphragm is influenced by the position of the heart rather than by that of the liver.

The electrocardiogram (Fig. 4) was characteristic of isolated dextrocardia, i.e., the complexes are upright in all leads except T in Lead I. Negative T waves in Lead I and sometimes in Lead II, as well as S-T segment deviations, may be found. There is no proof that the prognosis is made worse thereby, although the point is debatable.¹⁶ This electrocardiogram is easily distinguished from that of mirror-image dextrocardia. The proof of the supraventricular origin of the tachycardia lay in the response to carotid pressure (Fig. 5) and the similarity of the QRS complexes during and after the attack. "Auricular leads" (not shown) proved the auricular origin of at least one attack.

Certain other changes in the electrocardiogram, particularly the widening and slurring of the QRS waves, point to diffuse myocardial damage. The presence of coronary insufficiency and myocardial fibrosis, in addition to whatever congenital lesions she had, is likely because of the age of the patient and the frequency of the paroxysms of tachycardia which resulted in congestive failure.

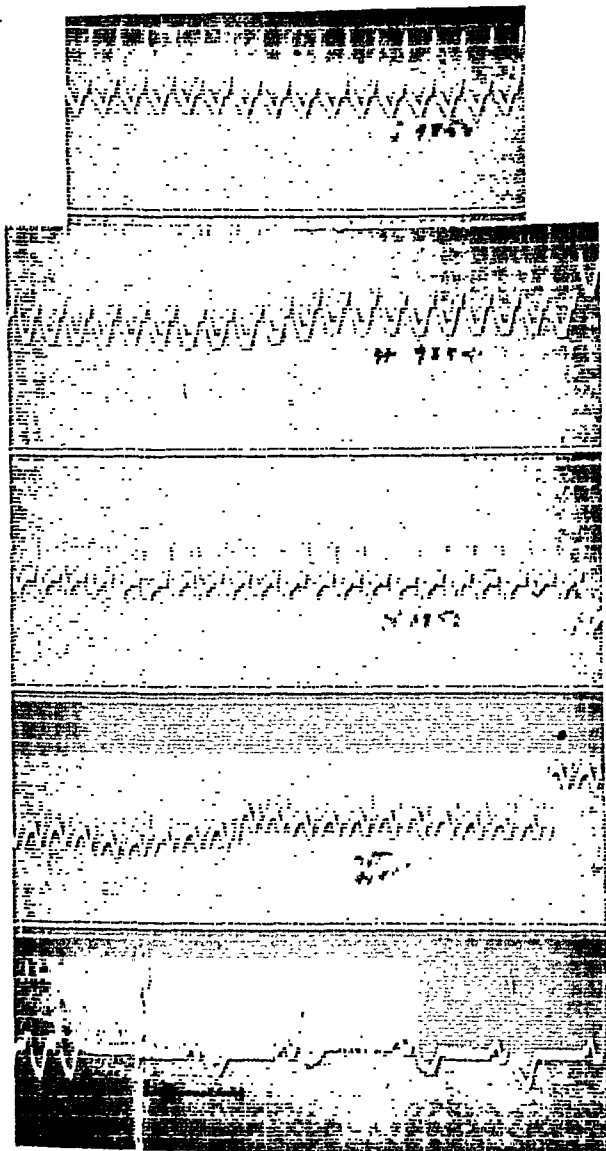


Fig. 5.—Electrocardiogram showing paroxysmal supraventricular tachycardia, with abrupt cessation on carotid pressure.

Finally, the nature of the lesion associated with the dextrocardia in this patient can only be guessed at. The murmurs were probably the result of either a pulmonary or an aortic lesion, and, since pulmonary stenosis or atresia is very common,⁷ we may safely guess that such an anomaly was present here.

SUMMARY

1. A case of congenital isolated dextrocardia, without "mirror-image" inversion of the chambers, but with signs of congenital heart disease and attacks of paroxysmal tachycardia is presented.

2. The expected noninversion of the heart chambers was supported by diodrast and electrocardiographic studies. The "apex" of the heart was shown to be formed by the right (venous) ventricle. The left-sided aortic arch and superior vena cava were also demonstrated by diodrast visualization.

3. The rarity of the long survival of the patient and of the attacks of paroxysmal tachycardia is noted.

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The monograph of Roesler¹⁶ contains about 350 references. The best review in English is that of S. S. Lichtman.⁷

PERSISTENT COMMON ATRIOVENTRICULAR OSTIUM

REPORT OF A CASE

VICENTE MORAGUES, M.D.

ST. LOUIS, Mo.

THIS congenital malformation of the heart is rare and is frequently associated with mongolism. Robinson,¹ in a recent review of the literature, found only thirty-nine cases, and many of them were only mentioned and not described. He added another case of his own. Of these forty cases, approximately one-half were in Mongolian idiots. Herein is presented another case of persistent ostium atrioventriculare commune in a child without mongolism or other major defects. This case is particularly interesting because there was an electrocardiographic and radiologic study.

CASE REPORT

The patient was a sixteen-month-old boy. He was born at full term, and breathed and cried spontaneously. The weight at birth was eight pounds. When three days old, the child was taken to the hospital because of dehydration, jaundice, and refusal to nurse at his mother's breast. At that time he was poorly developed, dyspneic, and cyanotic. On the right side of the head there was a hematoma the size of a hen's egg. Examination of the lungs was negative. The heart was of normal size, with no thrills and no murmurs. The rhythm was regular and the rate rapid. The child was given a transfusion, glucose, and a special feeding formula. He was discharged after eighteen days, much improved.

On the second admission, one month before death, the child appeared moderately dehydrated and extremely dyspneic. He had sat up at eight months but had not stood up nor crawled. He spoke his first word at eight months.

Physical Examination.—The patient was poorly nourished, poorly developed, moderately dehydrated, and markedly cyanotic. The temperature was 100° F., the respirations, 75 per minute, and the cardiac rate, 200 per minute. The chest had a pigeon breast appearance, with marked precordial bulging, mostly on the left side. The sternum was deformed and convex in shape. The apex impulse was diffuse and heaving. Numerous fine, crepitant râles were heard throughout both sides of the chest. The cardiac dullness was greatly increased; the left border of the heart was in the anterior axillary line. There were numerous murmurs over the precordium, and the rate was so rapid and the tones so loud that differentiation was impossible. The abdomen was scaphoid. The aortic pulsation was prominent. The edge of the liver was palpable and percussible three fingerbreaths below the costal margin.

Electrocardiogram.—The rate was 150 per minute and the rhythm regular. The P-R interval was 0.16 second. The QRS complexes were diphasic in all leads. The main deflections were downward in Lead I and upward in Lead III. The initial deflection was upward in Lead IVR and Lead IVF. P₁ and P₂ were prominent. P₂ was diphasic. The T waves were upright in all leads. The S-T segment take-off was 2 mm. low in Lead IVR and 2 mm. high in Lead IVF (Fig. 1). The electrocardiographic diagnosis was: (1) sinus tachycardia, (2) auricular hypertrophy, and (3) right axis deviation.

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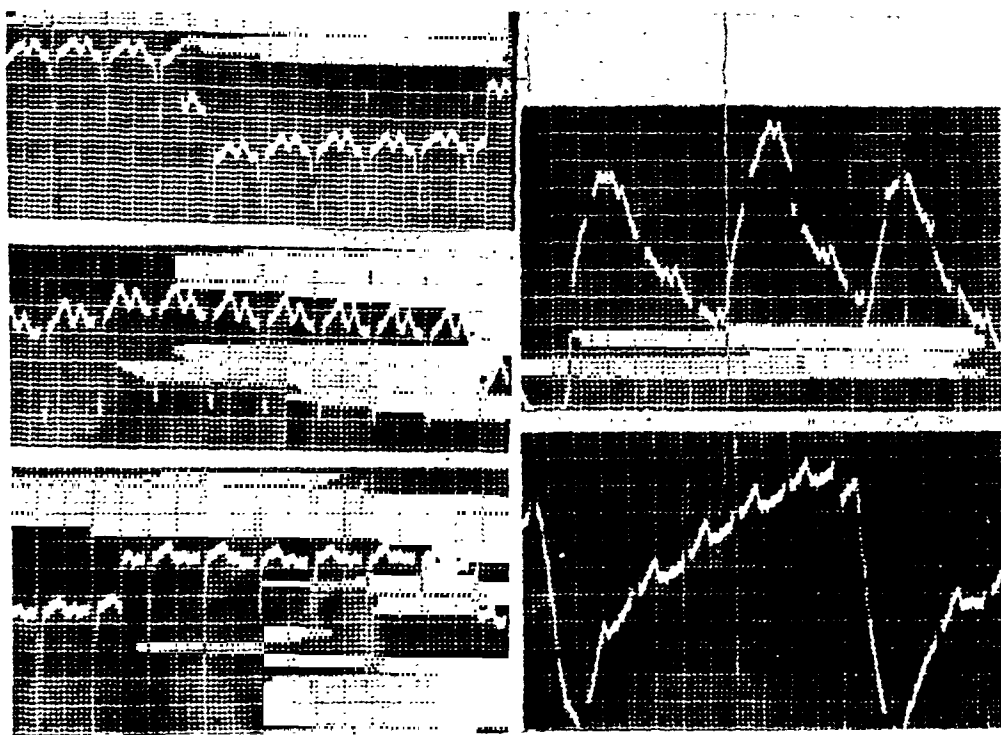


Fig. 1.—Electrocardiogram showing tachycardia, prominence of P_1 and P_2 , and a diphasic P_2 , right axis deviation.



Fig. 2.—Roentgenogram showing marked enlargement of the cardiac outline and marked pulmonary congestion.



Fig. 3.—Left atrium and left ventricle. Common ostium with valve leaflets going through it.



Fig. 4.—Right atrium and right ventricle. Perforations in the interauricular septum.

Roentgenologic examination (Fig. 2) revealed an enormously enlarged cardiac shadow, with the left border extending to the axillary margin and the right border far to the right of the midline. There was also marked pulmonary congestion.

Laboratory Data.—The hemoglobin was 13 Gm., the erythrocyte count, 4,000,000, and the leucocyte count, 16,000. A differential leucocyte count showed 3 per cent metamyelocytes, 17 per cent nonsegmented polymorphonuclears, 52 per cent segmented polymorphonuclears, 2 per cent eosinophiles, 4 per cent monocytes, and 24 per cent lymphocytes.

Course in Hospital.—On the second day the patient's temperature was 102.5° F. He was cyanotic except when oxygen was being administered. On the fifth day his temperature was 102° F., and he had cyanosis and pronounced dyspnea. On the twentieth day his temperature was 102° F. He began to develop passive congestion and pulmonary edema, his temperature rose to 103.5° F., and his heart became irregular and rapid (155 per minute). He was very cyanotic and dyspneic, and died of congestive heart failure.

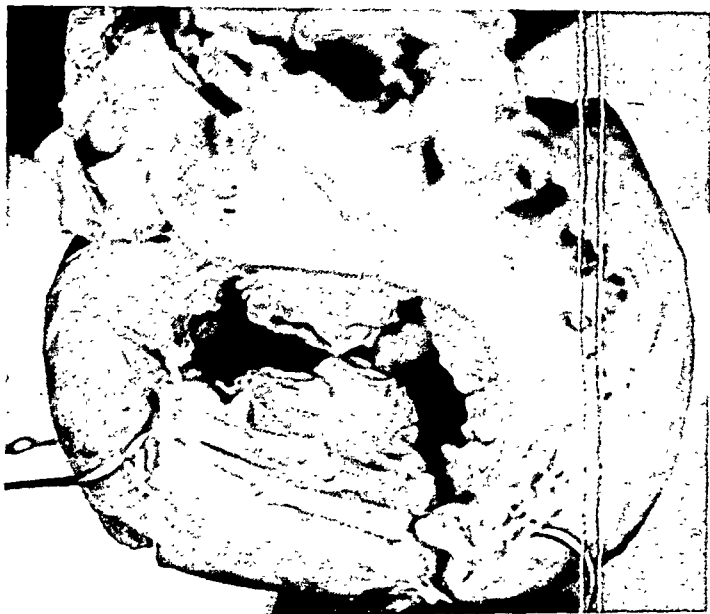


Fig. 5.—Common atrioventricular orifice with six valvular leaflets: two common leaflets (across midline), one leaflet in the left ventricle, and three in the right ventricle (two of these are rudimentary).

Autopsy.—The anatomic diagnoses were (1) persistent common atrioventricular ostium, (2) congestive heart failure, with hypertrophy and dilatation of the heart, (3) hydrothorax, (4) pulmonary congestion and edema, and (5) congestion of all viscera.

The heart weighed 119 grams. There was marked dilatation of the whole heart, but chiefly of the right side. The epicardium was thin and intact. The myocardium was markedly thickened, measuring 0.7 to 0.8 cm. in the right ventricle and 0.8 to 1.0 cm. in the left ventricle. The endocardium of the right ventricle was somewhat thickened, white, and opaque. In the left ventricle the endocardium was thin and intact. There was a large defect of the lower part of the auricular septum and the upper part of the ventricular septum (Figs. 3 and 4). This defect had a round shape and measured 2 cm. in diameter. Through the defect in the atrioventricular septum there were two large valve leaflets, one anteriorly and one posteriorly, going from one ventricle to the other. These two common leaflets had chordae tendineae attached to the upper, concave border of the interventricular septum. In the right ventricle, beside the two halves of the common cusps, there were a well-developed

leaflet and two small, rudimentary ones. In the left ventricle there was only one valve cusp in addition to the two left halves of the common leaflets (Fig. 5).

The foramen ovale was closed, but below the fossa ovalis, posteriorly, there were two small perforations of the auricular septum about 2 mm. in diameter. The aortic and pulmonary valves were essentially normal and measured 1.5 cm. in diameter.

According to Mall² and Gunn and Dieckmann, this developmental anomaly is caused by an arrest of growth of the heart in early intra-uterine life. This arrest of development has to do with the interauricular septum, the interventricular septum, and the endocardial cushions. This lack of development of the cardiac septa leaves a wide communication between the different chambers of the heart. During cardiac diastole, when the atrioventricular valves are open, the four chambers of the heart communicate with each other. During cardiac systole, when the A-V valves are closed, the two atria communicate with each other and the two ventricles with each other.

SUMMARY

A case of persistent ostium atrioventriculare commune is presented. Forty cases have been mentioned or described in the literature, and about half of these were associated with mongolism.

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AURICULAR STANDSTILL

VERNE S. CAVINESS, M.D., RALEIGH, N. C.

THE sinoauricular node, the pacemaker of the heart, was discovered by Keith and Flack, in 1907. It is at the end of the sulcus terminalis at the junction of the superior vena cava and the right auricle. It consists of nerve cells, nerve fibers, and heart muscle cells, imbedded in fibrous tissue. The nerve fibers are connected with the vagus nerves and the sympathetic trunks. The blood supply is rich and is received through a coronary artery branch. Sudden death has been reported from the occlusion by a syphilitic process of the mouth of this artery in the aorta.

MISSED BEATS

Disturbances in the sinoauricular node appear to be quite infrequent. When present, they are usually of short duration.¹ Sinoauricular block is the usual abnormality and is characterized by missed beats which should be differentiated from extrasystoles.

Sinoauricular block² produces a pause in the cardiac rhythm, and, because of the lack of the compensatory pause which follows extrasystoles, it is usually of less duration than two cardiac cycles. It may occur in healthy persons, e.g., athletes, after strenuous exertion, or after excitement. In children^{2, 3, 5} it may follow severe infections, such as diphtheria or rheumatic infections. Syphilis is an occasional cause. The most frequent cause is poisoning by digitalis. Quinidine⁴ may be a factor, especially when given with large doses of digitalis. Nervous exhaustion appears to be a contributing factor. It is not affected by strychnine, bromides, or theobromine.⁶ Nitrites and atropine tend to decrease the frequency of missed beats. Exertion appears to have a similar influence on some patients. Excessive smoking has been alleged by one observer to produce sinoauricular block.

Sinoauricular block is not to be confused with sinus bradycardia, in which the slow rate might suggest that alternate beats are being dropped. The gradual development of the bradycardia and the gradual recovery obviate the conclusion that there is a disturbance in rhythm.

AURICULAR STANDSTILL

Sinoauricular block in its most severe form is termed auricular standstill. This is a very rare condition. In 1939, Rosenbaum and Levine⁷ found eight cases in the literature and added a like number from the Massachusetts General Hospital. They added four possible cases to each group. No additional cases appear to have been reported.

Auricular standstill can be diagnosed only by the electrocardiogram.

There is no evidence of auricular activity, and the ventricles beat with a regular, independent rhythm. The mortality is very high, probably because of the degree of digitalis poisoning required to produce auricular standstill. It is not known whether there is a total blockage of transmission of impulses or whether impulses are not formed.

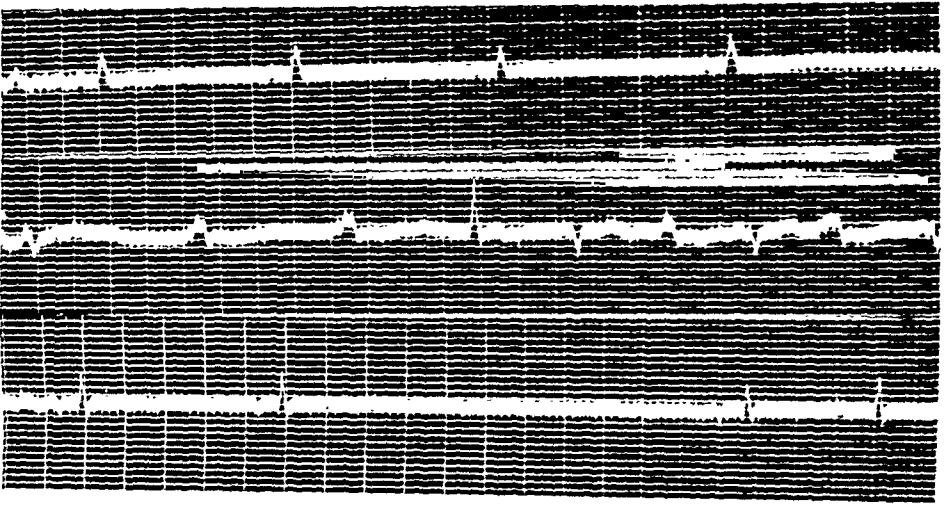


Fig. 1.—Mrs. L., May 4, 1941. Toxic digitalis effect: bradycardia, auricular and ventricular extrasystoles; Lead II shows only one normal beat and it appears to follow a P wave; Lead III shows a long interval, $2\frac{1}{2}$ seconds, of auricular and ventricular inactivity.

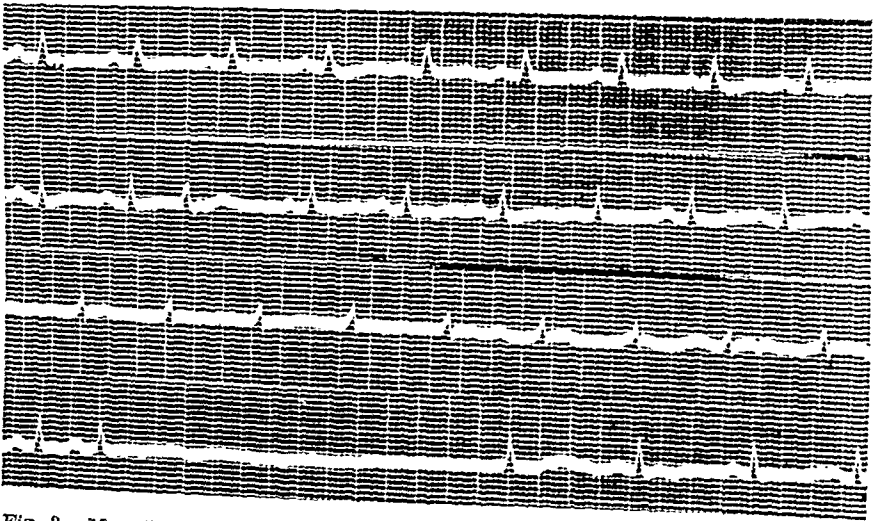


Fig. 2.—Mrs. L., May 8, 1941. Digitalis stopped and rhythm improved; P waves almost entirely absent in Lead III; Lead IV shows a period of $2\frac{1}{4}$ seconds of auricular and ventricular inactivity.

It appears likely that the condition is much more frequent than would be indicated by statistics: it is probable that many unexplained sudden deaths during digitalis therapy are caused by auricular standstill. Various factors, including digitalis poisoning, might account for failure of the ventricles to develop an independent rhythm.

Rest is often the best form of therapy and should be used far more than appears at times to be possible. Digitalis is a good crutch for a damaged heart, but it is also a very dangerous and poisonous drug when

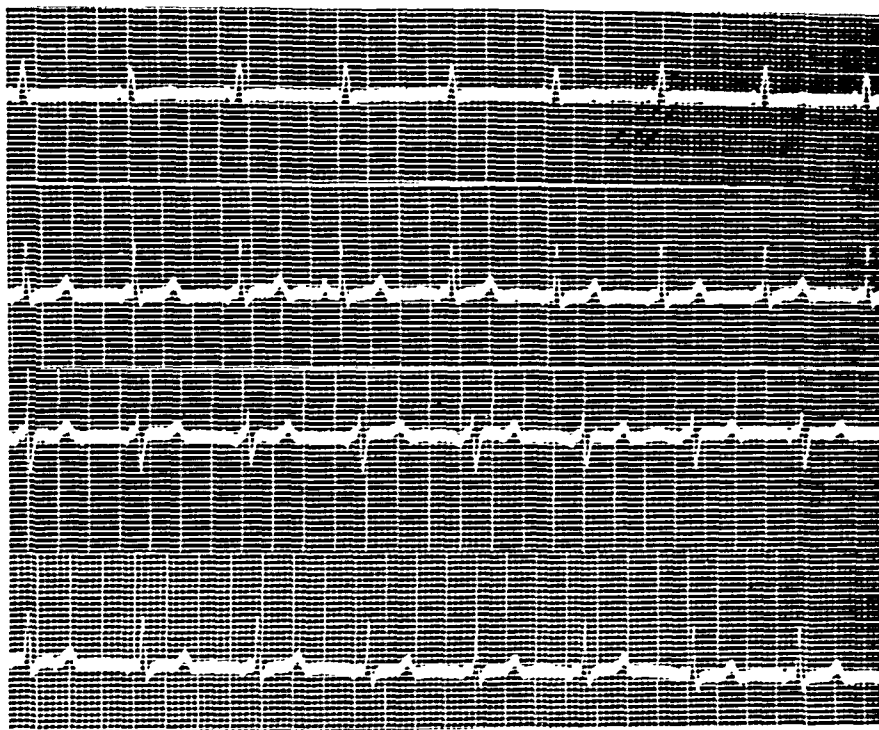


Fig. 3.—Mrs. L., June 9, 1941. No digitalis; conduction time shortened to half that of earlier tracings; rhythm regular.

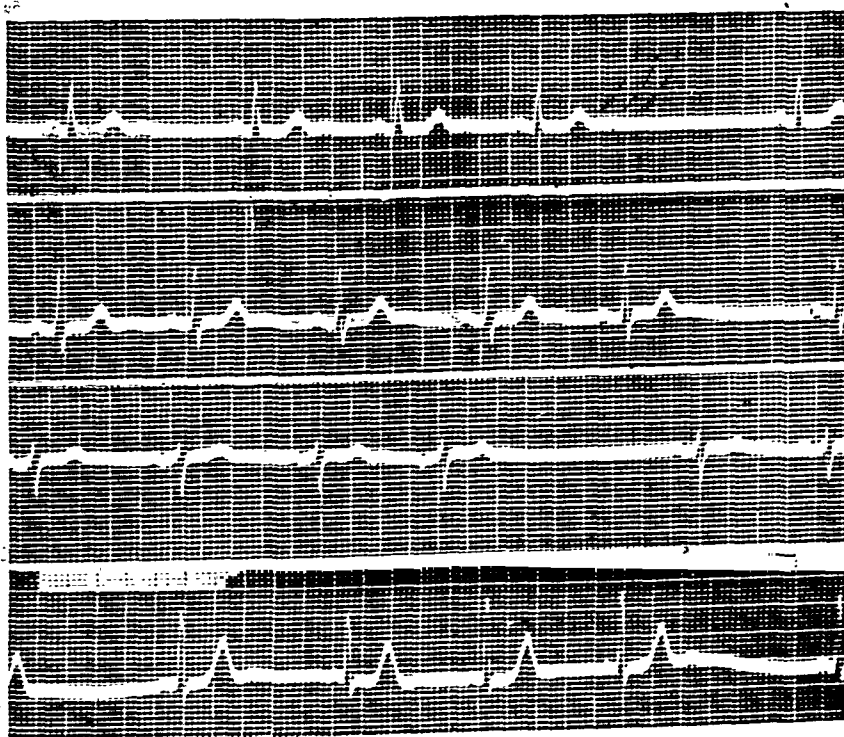


Fig. 4.—Miss H., May 19, 1941. Sinus rhythm; missed beats without full compensatory pause; this condition followed small doses of digitalis.

used in large doses. It is doubtful whether a large dose of digitalis is more effective than a small dose. When a small dose fails to improve the cardiac output, larger doses rarely, if ever, improve the results. Also, often it is impossible to slow the cardiac rate by digitalis; for various reasons, a rapid rate may be needed for an adequate circulation, and efforts to slow such a tachycardia by digitalis may be expected to end in disaster. Variability of individual susceptibility to the drug increases the danger from digitalis and necessitates greater care in its use.

Figs. 1, 2, and 3 are electrocardiograms of a patient who developed an irregular, rapid pulse after surgical drainage of her gall bladder. For three days she received, hypodermatically, sixteen ampoules of digifoline and ten ampoules of coramine. Part of the time she was given two ampoules of digifoline every three hours. The third tracing shows the result in her case of stopping digitalis. Death is the usual result.

Fig. 4 shows sinoauricular block with typical missed beats, not fully compensated, apparently caused by taking one cat unit of digitalis daily for five days. The digitalis was stopped, and, after several weeks, regular rhythm was gradually restored.

CONCLUSION

These two cases, one of auricular standstill and one of sinoauricular block, are quite interesting from the standpoint of rareness as well as etiology.

It is possible that auricular standstill may not be so rare as has been supposed. Adequate use of the electrocardiograph might show that this condition is quite common, not only as a terminal event, but also as a result of infections, digitalis, and strenuous exertion.

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Abstracts and Reviews

Selected Abstracts

Yanof, Z. A.: Blood Pyruvic Acid in Heart Disease. Arch. Int. Med. 69: 1005, 1942.

There is a rise above normal of pyruvic acid in the blood of persons with heart failure. This elevation approximates the degree of failure.

AUTHOR.

Herrmann, G., Decherd, G. M., and Calvin, D. B.: The Application of Blood Volume Studies to the Theory of the Mechanism of Diuresis. Tr. A. Am. Physicians 56: 298, 1941.

Serial blood plasma volume studies following the intravenous injection of diuretics, aminophyllin, salyrgan, mercupurin, and digoxin have yielded further evidence as to the various mechanisms that initiate and accompany diuresis.

With the mercurials and the xanthines given intravenously there seems to be definitely primary renal effects and probably subsequent secondary extrarenal effects.

It is not possible by these present studies to localize absolutely the site of the renal or extrarenal action. Diuresis is not dependent upon the rise in blood plasma volume. It may continue with falling blood plasma volumes and drop off with rising blood plasma volumes. At any one time the blood plasma volume is the resultant of urine excretion through the kidney and movement of fluid from or to the tissue interstices.

The total blood volume shifts usually are not commensurate with the volumes of urine excreted.

AUTHORS.

Nahum, L. H., Hoff, H. E., and Kaufman, W.: The Nature of the S Complex of the Electrocardiogram. Am. J. Physiol. 136: 726, 1942.

The downstroke of S_2 develops with the complete activation of the posterior surface of the left ventricle while a portion of the anterior surface of the right ventricle is not yet active.

The upstroke of S_2 occurs when the remainder of the anterior surface of the right ventricle becomes active and restores isopotentiality.

The same sequence of ventricular excitation explains the presence of an S_2 in the ventricular extrasystole.

S_1 probably arises from a similar sequence of excitation in the anterior left and posterior right ventricles.

AUTHORS.

Groedel, F. M., Kisch, B., and Reichert, P.: Changes in the Standard Electrocardiogram and the Chest Leads During the First Stages of Life. *Cardiologia* 6: 1, 1942.

While in the adult with normal heart conditions two different chest electrocardiograms, the left and the right, always exist, the newborn seems to show immediately after birth, usually over the whole thorax, only one pattern, that of the

right chest electrocardiogram. This pattern changes in the left axilla line generally after a few hours, but not infrequently after days, into that of the left electrocardiogram. On the contrary the chest electrocardiogram led from the sternum does not change its character during the first life span, only the coefficient R-height to S-height alters, insofar as, during the first days of life, the coefficient resembles that found in older adults, while it changes later on to that found in children and younger adults.

AUTHORS.

Groedel, F. M., and Kisch, B.: Morgagni-Adams-Stokes Syndrome: What Does It Represent? *Cardiologia* 6: 43, 1942.

The M.A.S. syndrome is a condition of attacks of unconsciousness, with or without the occurrence of convulsions and incontinence of urine and bowels, caused by an acute ischemia of the central nervous system. The causative factors of such attacks are always acute disturbances of the heart action leading to an insufficient blood supply to the cerebrum. We observe the syndrome occurring in two groups of heart disease, in cases suffering from heart block and in patients suffering from tachycardia or salvos of ventricular extrasystoles or attacks of ventricular fibrillation. Abortive cases are also very frequent. These patients likewise suffer from different types of short attacks of tachycardia, paroxysmal auricular fibrillation and attacks of extrasystoles, leading only to a lesser degree of cerebral ischemia and, therefore, the patients are complaining about only fainting-like spells. We never observed a case of M.A.S. syndrome due to sinus bradycardia, although such cases are referred to in the French literature.

AUTHORS.

Hermann, R., and Decherd, G. M., Jr.: Tachycardias: Diagnosis and Treatment. *New Orleans M. & S. J.* 94: 417, 1942.

Sinus tachycardia is due to a variety of causes and sometimes will be slowed by vagus stimulation either through the carotid sinus, or by drugs such as pilocarpine or prostigmine or neosynephrin. Digitalization is effective in cases with heart failure, indirectly by improving the circulatory efficiency, or directly by precipitating fibrillation and A.V. block.

Paroxysmal tachycardias are briefly discussed from the clinical and electrocardiographic points of view. Those from a supraventricular focus are managed by trying first the effects of reflex vagal stimulation. Acetyl-Beta-methylcholine or prostigmine methyl sulphate are sometimes successful. Quinidine has been used as have various digitalis preparations as digoxin, digitonins or lanatoside C or digitalis extracts, either by mouth or intravenously. Quinidine or potassium salts are used prophylactically. For the paroxysms from a ventricular focus, due usually to a myocardial infarction, quinidine is the only drug to be recommended.

Tachycardias due to circus mechanisms, auricular flutter and auricular fibrillation are described. Digitalization converts a flutter to a fibrillation, and cinchonization is usually then necessary to establish a sinus rhythm. Quinidine alone without preliminary digitalization is often efficacious in auricular fibrillation cases of short duration and it is justifiable to use quinidine in an attempt to establish the normal rhythm. Digitalis usually controls the ventricular rate when the auricles are fibrillating.

For details of diagnosis and dosage the original may be consulted.

AUTHORS.

Stein, W., and Uhr, J. S.: Congenital Heart Block: Report of a Case. *Brit. Heart J.* 4: 7, 1942.

Because of its comparative rarity, another case of congenital heart block occurring in a white three-year-old female child is added to the literature. The ac-

cidental manner in which the anomaly was discovered after the youngster had been hospitalized and operated upon for a right acute mastoiditis is related.

The pathology of the abnormal embryological development of a patent inter-ventricular septum and its association with congenital heart block is discussed.

AUTHORS.

Urbach, E., Loew, A., and Gottlieb, P. M.: *Bronchial Asthma and Cardiopathy*. *Cardiologia* 6: 13, 1942.

Damage to the heart will often develop during the course of an asthma of long duration. This involves the myocardium, never the endocardium. For hemodynamic reasons, the right ventricle is affected first. But not infrequently, especially in older asthmatics, the left heart may become affected, the disorder being manifested clinically as angina. Attention has been drawn to the possible etiological relationship between bronchial asthma and coronary disease. Recognition of the cardiac involvement and understanding of its pathogenesis are of importance in therapy. The authors point out the value of electrocardiograms in every case of asthma. These should be taken not only in the free intervals, but also after effort, and if possible, during the attack of asthma. The theory is expressed that electrocardiographic changes occurring only during asthmatic attacks are caused by myocardial anoxia.

Emphasis is placed on the necessity of roentgenological examinations for the early determination of stasis in the lesser circulation as a sign of associated involvement of the heart. The point is stressed that remarkable results are achieved by the intravenous administration of strophanthin, aminophylline, and glucose in cases of asthma where involvement of the heart cannot be demonstrated by clinical and electrocardiographic methods.

AUTHORS.

Duchosal, P. W., and Henny, G.: *Angina Pectoris and Hyperthyroidism*. *Cardiologia* 5: 372, 1941.

A 50-year-old woman had all signs of a hyperthyrosis, the appearance of which was noted in the menopause. Progressive emaciation, increased metabolic rate, and attacks of typical angina pectoris in rapid succession were experienced. Treatment with lugol brought immediate improvement and temporary disappearance of the angina pectoris. Strumectomy was performed, shortly after which the patient died. The electrocardiograms showed very great variability in the course of the hyperthyreotic periods. The characteristic change was an extreme but temporary increase of the S-T piece. This change appeared independently from the angina pectoris, usually, however, following exertion. It was also observed after the apnea and hyperpnea tests, however, spontaneously.

The anatomic examination showed the coronary arteries and their branches into the capillaries to be fully intact. The myocardium was the seat of a large number of degenerative centers of especial appearance. They reminded one of the toxic conditioned changes in the course of tuberculosis. The anatomical examination of the goiter showed two very small adenomas of Basedow infected tissues to be the only cause of this severe thyreotoxicosis.

An explanation of the angina pectoris, founded on the hypothesis of the factor P after Lewis, is given.

AUTHORS.

Raab, W.: *Abnormal Suprarenal Discharges in Angina Pectoris and Their Control by X-ray Therapy*. *J. Clin. Endocrinol.* 1: 977, 1941.

Adrenocortical (AC) compounds, which consist of adrenalin combined with cortical sterols were quantitatively determined by a chemical method in the blood of individuals with and without angina pectoris.

In angina patients the blood AC level, although generally normal at rest, showed abnormally intense, sharp elevations after physical exercise. These elevations persisted for several minutes. The AC compounds which were discharged into the blood stream during physical exercise were particularly rich in adrenalin.

Therapeutic roentgen irradiation of the suprarenal glands, if successful, resulted in disappearance of the abrupt AC discharges on effort, coinciding with complete or almost complete disappearance of the subjective anginal symptoms for periods of several months.

The significance of these observations is discussed from the point of view of the theory that angina upon effort is caused by the specific anoxiating effect of sudden suprarenal discharges upon the heart muscle whose oxygen supply is inadequate, due to sclerosis of the coronary arteries and their inability to dilate adequately.

AUTHOR.

Pool, W.: *Cardiometric Studies on Children. III. Report of a Case of Incomplete Heart Block Due to Vagal Effect.* Arch. Int. Med. 69: 1040, 1942.

A case of persistent functional heart block apparently due to vagal influence is presented. Three previously described cases of such disturbance are reviewed.

The frequency of occurrence of this phenomenon in normal adolescents is low. It was encountered only once in 2,400 electrocardiograms made on normal persons between the ages of 12 and 20.

Body position, body activity and respiration were found to have a definite effect on the duration of the PR interval in the case reported here. Respiration also affected the intensity and audibility of a third heart sound, or auricular sound.

Observations pertaining to the effect on the heart of experimental excitation of the vagus nerve are reviewed. A possible explanation of the origin of functional heart block is suggested in the light of these observations.

AUTHOR.

Hayes, R. M., and Gibson, S.: *An Evaluation of Rheumatic Nodules in Children: A Clinical Study of 167 Cases.* J. A. M. A. 119: 554, 1942.

Of 167 children with rheumatic nodules, 86 were boys and 81 girls. The age incidence of patients with nodules closely paralleled the age incidence in the group with rheumatic infection in general. Nodules were found in many regions, the most frequent locations being the elbows, knees, scalp, knuckles, malleoli, and vertebral spines. Nodules on the extremities tended to be symmetrical in their distribution. The duration of nodules varied from a few days to several months. Other rheumatic phenomena were present in every case. Rheumatic heart disease was found in 163 cases. Fifty-two patients (31 per cent) died. The number of nodules in the individual case was not found to be important in determining the prognosis.

AUTHORS.

Schwartz, S. P., and Marcus, H.: *The Electrocardiogram in Pulmonary Tuberculosis. I. The Clinical Significance of Concordant Inverted Initial Ventricular Deflections in Patients With Chronic Pulmonary Tuberculosis.* Am. Rev. Tuberc. 46: 35, 1942.

A study was made of the clinical significance of electrocardiograms showing a concordant type of inverted initial ventricular deflections in the standard leads in 7 patients with chronic pulmonary tuberculosis.

In 2 patients, the appearance of this pattern was associated with signs of congestive heart failure and recognizable enlargement of the heart as judged from

comparison of roentgenograms and fluoroscopic examination. In 5 patients the appearance of this pattern was found to be associated with symptoms of severe dyspnea and cyanosis but with a relatively small heart in the roentgenograms.

In 3 patients, in addition to the downwardly directed QRS complexes there was enlargement of the P-waves in Leads II and III and abnormal variation in the RS-T segment in Leads II, III, and IV.

In 6 of the patients who came to necropsy this electrocardiographic pattern was found to be associated with either hypertrophy alone, hypertrophy and dilatation, or dilatation without hypertrophy of the right ventricle and occasionally the right auricle.

These correlated observations suggest that in patients with chronic pulmonary tuberculosis the appearance of downwardly directed deflections of the QRS complex are an index of changes in the muscle mass or the size of the right ventricle causing a rotation of the heart around its longitudinal axis.

Since respiratory distress and increasing cyanosis in patients with chronic pulmonary tuberculosis may be due either to the progression of the pulmonary lesion or to right heart failure in the absence of signs of congestion, this electrocardiographic pattern may be the only clue that the symptoms are the result of cardiac embarrassment.

This pattern being persistent and irreversible, its presence is of ominous prognostic significance. None of the patients with chronic pulmonary tuberculosis who showed it lived longer than one year.

AUTHORS.

Grollman, A., and Williams, J. R., Jr.: Experimental Hypertension in the Rat. *Am. J. M. Sc.* 204: 73, 1942.

A variety of procedures is outlined by which it is possible to induce chronic hypertension in the rat. The most practical of these procedures consists in applying silk to the kidneys. This is accompanied by relatively low operative mortality and usually results in a permanent elevation of pressure to hypertensive levels. The blood pressure responds to various other operative procedures on the kidneys are described.

AUTHORS.

Chasis, H., Goldring, W., and Smith, H. W.: Blood Pressure Reduction Associated With Pyrogenic Reaction in Hypertensive Subjects. *J. Clin. Investigation* 21: 369, 1942.

Blood pressure can be reduced significantly in hypertensive subjects by the intravenous administration of pyrogenic material (pyrogenic inulin, triple typhoid vaccine, tyrosinase), and it can be maintained at reduced levels by the repeated injections of this material. This hypotensive effect can be obtained without a rise in body temperature by premedication with amidopyrine.

The mechanism responsible for the persistent blood pressure reduction is unknown, but, from the more immediate effects of pyrogen, it appears to be attributable in part to an adverse or asthenic action on the cardiovascular system, rather than a correction of the fundamental disturbance underlying the hypertensive process.

One instance of a marked reduction in blood pressure in a hypertensive subject during a postcystoscopic febrile reaction is illustrated. Such reactions are reported to be attributable to a transient *B. coli* bacteremia, and the reduction of blood pressure here, and in other acute infections, may be associated with the pyrogenic reaction associated with the infection.

Whenever the blood pressure of a hypertensive subject is reduced by the parenteral administration of a foreign organic material, this pyrogenic type of

response should be excluded before a specific hypotensive property is attributed to the agent used. And any pyrogenic material should be administered cautiously, since it may induce an alarming degree of peripheral circulatory failure, as illustrated by one of our subjects.

AUTHORS.

Kempf, G. F., and Page, I. H.: Production of Experimental Hypertension and the Indirect Determination of Systolic Arterial Pressure in Rats. *J. Lab. & Clin. Med.* 27: 1192, 1942.

Silk perinephritis and constriction of the renal artery by a silk thread both elicit arterial hypertension in rats of a degree sufficient for assay of renal anti-pressor extracts. The preparation of hypertensive rats by these methods is described.

The method of Williams, Harrison, and Grollman for measurement of systolic blood pressure has been modified to increase its effectiveness.

AUTHORS.

Kaiser, I. H.: The Specificity of Periarterial Fibrosis of the Spleen in Disseminated Lupus Erythematosus. *Bull. Johns Hopkins Hosp.* 71: 31, 1942.

The splenic pathology in 18 cases of disseminated lupus erythematosus is summarized. Perisplenitis and periarterial fibrosis were the commonly observed lesions. Periarterial fibrosis was found in 15 of the 18 cases in this series.

The perisplenitis presents no characteristics by which it may be differentiated from that commonly seen in other conditions.

Periarterial fibrosis is defined herein as the occurrence of at least three separated layers of the normally densely packed periarterial collagen of penicillary and follicular arteries, in such a manner as to give the typical ringed appearance. The collagen is frequently hyaline and granular eosinophilic material may be found continuous with it. The process apparently is an alteration of collagen independent of necrosis or inflammation. No early or intermediate stages have been observed.

In the control series of 1679 splenic sections periarterial fibrosis occurred in 53 cases, an incidence of 3.2 per cent. No evidence of the occurrence of disseminated lupus erythematosus could be found in any of these cases.

Periarterial fibrosis occurred in 4 cases of essential thrombocytopenic purpura out of 13 examined, an incidence of 31 per cent. This is the only group besides the cases of disseminated lupus erythematosus which significantly differed from the control series.

The splenic lesions of disseminated lupus erythematosus are not pathognomonic of that disease, although periarterial fibrosis occurs in a very high proportion of the cases. There are no known characteristics of the splenic periarterial fibrosis found in disseminated lupus erythematosus which will distinguish it from that found in other conditions. In view of its frequent occurrence in disseminated lupus erythematosus, however, the discovery of the lesion at autopsy should raise a suspicion of disseminated lupus erythematosus and provide impetus for further investigation. When found in association with the other familiar stigmata of disseminated lupus erythematosus periarterial fibrosis in the spleen provides corroborative evidence.

AUTHOR.

Hess, L.: On the Crista Terminalis. *Cardiologia* 5: 388, 1941.

It is suggested that the Crista terminalis may play a peculiar and not unimportant role during the systole of the auricle.

AUTHOR.

Lake, M., Pratt, G. H., and Wright, I. S.: *Arteriosclerosis and Varicose Veins: Occupational Activities and Other Factors. A Study of 536 Persons, Divided Into Age Groups, Who Had Been Sitting, Standing, Walking or Climbing Stairs for Ten Years or More at Their Work.* J. A. M. A. 119: 696, 1942.

Men had a higher incidence of arterial disease than did women of the same ages who had been employed at similar occupations an equal length of time. Among the younger men (age group 40 to 49 years), stair climbing apparently produced a significantly higher incidence of arteriosclerosis than did standing, sitting, or walking. No significant difference could be established among the last three classifications. Over the age of 50 there were no significant differences in the incidence of arterial disease in any of these classifications.

The use of alcohol and tobacco did not influence the incidence of arteriosclerosis in the series studied.

There was a definite relation in both sexes between the incidence of hypertension and of arteriosclerosis of the lower extremities.

Women showed a much higher incidence of varicose veins than did men employed in the same occupations. This difference held true even when the factor of pregnancy was removed from the data. Women who had been pregnant showed a higher incidence of varicose veins than women who had never been pregnant. Varicose veins were extremely common among the working women of this series.

Women who stood or walked showed a much higher incidence of varicose veins than those who sat at their work.

This difference was not found in men.

There was a higher incidence of arteriosclerosis of the leg arteries in men with varicose veins. This difference was not statistically established in women.

AUTHORS.

Hertzman, A. B., and Roth, L. W.: *The Vasomotor Components in the Vascular Reactions in the Finger to Cold.* Am. J. Physiol. 136: 669, 1942.

The vascular reactions in the finger to chilling have been examined by means of the photoelectric plethysmograph. Analysis of these reactions was concerned with the role of the vasomotor reflexes.

The initial immediate constriction on application of cold is due to vasoconstrictor reflexes on which is superimposed somewhat later the direct constrictor action of cold. Evidence: Accompanying constriction occurs also in the warm control fingers of the same and opposite hands, but the constriction is usually more intense in the chilled finger.

If a vasoconstrictor reflex is not elicited in the control fingers by an application of moderate cold, the constriction in the chilled finger occurs in a gradual progressive manner, as in the forehead skin, due to the direct constrictor effect of cold on the vessels.

The reactive dilatation, which follows in the chilled finger within three to eight minutes after the application of cold, occurs independently of the vasomotor system. Evidence: The dilatation may be limited to the chilled finger and may occur there when the vasoconstrictor tone is high in the control fingers.

Vasoconstrictor reflexes were elicited in the chilled finger during the reactive dilatation in some experiments, while in other instances definite evidence of vasoconstrictor paralysis in the chilled finger was obtained.

AUTHORS.

Hertzman, A. B., and Roth, L. W.: *The Reactions of the Digital Artery and Minute Pad Arteries to Local Cold.* Am. J. Physiol. 136: 680, 1942.

The selective effects of local cold on the terminal pad vessels and the digital artery of the chilled finger were demonstrated by means of photoelectric plethysmographs.

The digital artery does not participate in the vasoconstrictor reflexes elicited by the cold. Its later constriction during the continued application of cold appears to be due to the direct effects of the fall in temperature on the artery.

The reactive dilatation which appears during the application of cold is limited to the minute pad vessels and does not involve the digital artery until the resultant rise in finger temperature permits relaxation of this artery.

The effects of these reactions on the propagation of the pulse in the finger's arterial system were studied by recording the pad pulses with high frequency galvanometers.

In the usual experiment, the time relations and form of the pad pulses in the chilled finger were altered only moderately and in the direction which would be predicted from the relative participation of the pad and digital arteries in the reactions to cold.

In a few normal subjects, the reactive dilatation produced a pad pulse similar to that seen in chronic hypertension, thus suggesting that one of the factors responsible for the change in pad pulse form in hypertension may be the shunting of blood through direct arterio-venous communications.

AUTHORS.

Nylin, V. G., and Malmstrom, G.: Further Investigation Concerning the Interpretation of Prolonged Circulation Time in Cardiology. *Cardiologia* 5: 332, 1941.

Research into the circulation time by means of the decholin method showed that in 48 healthy persons the time until the first taste perception set in varies between 8 and 21 seconds, an average of 12 seconds, showing a standard deviation of 3.6. The period of taste perception varies between 7 and 24 seconds, an average of 12.8 seconds, and showed a standard deviation of 4.0.

Examination of the same healthy persons at the same time demonstrated that the circulation time in a recumbent position, when the rest blood quantity is larger, was longer; in a standing position, when the rest blood quantity is smaller, the circulation time was shorter.

This change in the circulation time by altered body position cannot be due to an increase in the minute volume on the basis of "getting up work." The work test demands relatively very heavy work to produce the same shortening of the circulation time as in getting up. Neither can it be explained either by hydrostatic blood dislocation phenomena or by alteration of the pulse frequency, the pulse and minute volume appearing on such alterations of position. The latter fall entirely out of account or are considerably reduced by a mechanical ligaturing of the thigh before the position change. On the other hand, the circulation time on arising from a recumbent position is also shortened after the thigh has been ligatured. The shortening appears to be quantitatively not smaller.

There appears to be a definite correlation between the circulation time and the size of the heart in compensated cases of cardiovascular disease.

AUTHORS.

Hirsch, V. S.: Concerning the Regulation of Blood Flow in the Coronary Artery System of Man and the Possibility of Its Histologic Proof. *Cardiologia* 6: 31, 1942.

In the human coronary artery system there are small branches, the walls of which contain layers of so-called epitheloid cells, such as have been variously described in the jugular or cushion arteries of other vessel provinces.

The arteriovenous transverse connections supposed from physiologic and clinical facts and demonstrated 30 years ago were confirmed histologically by the proof of arteriovenous anastomoses.

According to our findings there are peculiar relations of the so-called epitheloid cells to the elastic elements of the vessel wall. The proof of these cells, sometimes in the one, sometimes in the other sector of the vessel wall, sometimes inside, sometimes outside a closed elastica interna, and the fact that the elastica itself resolves into lines and dots point to a strong plasticity not only of the epitheloid cells but also of the elastic elements as well. Furthermore, the near local relation of the regulatory arrangement of the nervous apparatus is remarkable.

Generally speaking, the previous observations of blood circulation regulators in both man and animals ensued more or less accidentally, our experiments, however, gave a definite proof of the conditions of the possibility of their delineation. The evidently very sensitive formations found in the small arteries are only definitely provable histologically when one succeeds in fixing the blood before firm coagulation sets in. The result of our research appears, from a general point of view, of great importance for the critical estimation of the observable normal formation of small vessels in a cadaver and in a greater measure of pathologic changes.

AUTHOR.

Nicholson, J. C.: Cardiac Massage. Brit. M. J. 1: 385, 1942.

The author emphasizes the extreme urgency of this condition, which may arise in any operation, however trivial. The decision of whether to attempt cardiac massage must be made at once, and one must act with utmost speed. Only if this is done is any good likely to ensue.

McCULLOCH.

Egan, W. J.: Cardiovascular Disease in Industry. Wisconsin M. J. 41: 217, 1942.

The writer reports his experiences in the management of the industrial personnel. It is his belief that he has reduced the rate of mortality of the employees. He is known to have definitely reduced absenteeism from illness.

AUTHOR.

Lowry, E. F.: Evaluation of Heart Signs in Navy Recruiting. Mil. Surgeon 90: 37, 1942.

The author describes briefly the usual signs of borderline cardiac disease and disturbances in the recruits.

McCULLOCH.

Bramwell, C.: Wartime Problems of a Cardiologist (Finlayson Memorial Lecture). Glasgow M. J. 19: 1, 1942.

A useful résumé in classical form by a real master of the common problems facing selective service boards and cardiologists in the armed service. The problem of accurate diagnosis and classification is really important to the draftee and the service which the examining physician represents.

McCULLOCH.

Allen, C. R., Stutzman, J. W., Slocum, H. C., and Orth, O. S.: Protection From Cyclopropane-Epinephrine Tachycardia by Various Drugs. Anesthesiology 2: 503, 1941.

Procaine, carbon dioxide, quinidine, morphine, ergotamine, F 883 (diethyl-amino-methyl-benzo-dioxane), and yohimbine have been studied for the prevention of cyclopropane-epinephrine tachycardia. These agents are all protective in proper dosages. The effective amounts per kilogram when administered intravenously are: procaine, 16 mg.; quinidine, 15 mg.; ergotamine, $\frac{1}{6}$ mg.; F 883, 2.0 mg.; and yohimbine, 0.2 mg. The morphine dose was 8 mg. per kg. when given subcutaneously. Twenty to 24 per cent carbon dioxide in the anesthetic mixture also gave protection.

It is believed that procaine, carbon dioxide, and quinidine give protection from cyclopropane epinephrine tachycardia because of myocardial depression; F 883 and ergotamine, by their sympathicolytic action; yohimbine, through its adrenolytic action; and morphine, by producing either functional decerebration or myocardial depression.

AUTHORS.

Thienes, C. H., Greeley, P. O., and Guedel, A. E.: Cardiac Arrhythmias Under Cyclopropane Anesthesia. *Anesthesiology* 2: 611, 1941.

Cardiac arrhythmias occur in cyclopropane anesthesia. These arrhythmias appear at about the beginning of respiratory failure, and are typically of the nature of ventricular extrasystoles.

High concentrations of cyclopropane (50 to 75 per cent in alveolar air), or larger doses of atropine, abolish or minimize these arrhythmias in a large proportion of subjects.

Cyclopropane does not seem to be toxic to the heart, since extreme concentrations failed to produce changes in cardiac activity which we can interpret as muscle depression, except in the presence of anoxemia (experiments on the dog).

A-V nodal rhythm occurred in a small number of human and dog subjects at 70 per cent cyclopropane. Increasing the concentration to 100 per cent resulted in A-V nodal rhythm in most dogs.

An explanation of the effect of high concentrations of cyclopropane on cardiac arrhythmias is suggested.

AUTHORS.

Kaltreider, N. L., Meneely, G. R., and Allen, J. R.: The Effect of Epinephrine on the Volume of the Blood. *J. Clin. Investigation* 21: 339, 1942.

Measurements were made at rest of the volume of the blood and its components, and variations in the volumes were followed after the subcutaneous injection of 1 c.c. of epinephrine (1-1000). Further observations included measurements of the blood hemoglobin and viscosity, serum proteins, venous and arterial pressures, velocity of the blood, and pulse rate. These observations lead to the following conclusions:

1. In normal individuals, following the administration of epinephrine, there is a prompt and definite decrease in the plasma volume, which persists in most cases for at least 45 minutes. In the majority of cases there is a slight increase in the cell volume. These alterations are associated with an increase in blood hemoglobin and viscosity and serum proteins. Following the administration of the drug, the systolic pressure increased while the diastolic pressure fell slightly.

2. In individuals who have polycythemia vera with splenomegaly, epinephrine causes a definite decrease in the plasma volume, a moderate increase in cell volume with little change in the total volume.

3. After the injection of epinephrine into 2 individuals whose spleens had been removed, there was a decrease in both blood and plasma volumes, accompanied by a slight decrease in the cell volume.

4. The effects of severe exercise and of epinephrine on the components of the blood volume are similar.

L. W. ROTH.

Dale, U. D., and Jacques, L. B.: The Prevention of Experimental Thrombosis by Dicoumarin. *Canad. M. A. J.* 46: 546, 1942.

Intravenous injection of 3, 3 methylenebis (4-hydroxycoumarin), "dicoumarin," increases the prothrombin time of dogs. The administration of this substance in sufficient amounts prevents the formation of intravascular and extravascular thrombi.

This demonstrates an intimate connection between the clotting mechanism and the formation of thrombi (agglutination of platelets). Further, it provides an experimental basis for the clinical use of the material to prevent thrombosis.

Due to its cheapness, its long action, and the fact that it is active on oral administration, dicoumarin possesses many definite advantages for clinical use in the prevention of thrombosis. The long latent period before its effect is demonstrable and the impossibility of terminating this effect quickly may constitute disadvantages. Before its clinical use can be recommended, further studies regarding its toxicity should be undertaken.

AUTHORS.

Flaxman, N.: Digitalis in Arteriosclerotic (Coronary) Heart Failure With Normal Rhythm. J. A. M. A. 119: 252, 1942.

The action of digitalis on 51 patients with arteriosclerotic (coronary) heart failure with normal rhythm was studied.

The patients were divided into two groups: those with a normal rate (31 or 61 per cent) and those with sinus tachycardia (20 or 39 per cent).

Digitalis was most effective on those with isolated failure of the left ventricle and a normal rate, and least effective on those with combined ventricular failure and sinus tachycardia.

The action of digitalis is primarily on the myocardium and not on the cardiac rate, as noted by the mortality of 6.4 per cent in those with a normal rate and 60.0 per cent in those with sinus tachycardia.

The use of increased amounts of the newer digitalis, U. S. P. XI, only brought on early toxic reactions and had no effect on the mortality.

AUTHOR.

DeGraft, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics. J. A. M. A. 119: 998, 1942.

The lethal doses for six mercurial diuretics when injected intravenously in the cat so as to kill within twenty to thirty minutes are salyrgan-theophylline 1.11, mercupurin 0.83, mercurin 0.70, salyrgan 0.41, esidrone 0.24, and esidrone without theophylline 0.27. These values are in cubic centimeters per kilogram and have been adjusted to a mercury content of 40 mg. per c.c.

Previous treatment with oral ammonium chloride, oral phenobarbital, intravenous aminophylline, and intravenous digitaline Nativelle had no effect on the lethal dose of mercupurin.

At least in the case of mercupurin, the lethal dose is smaller the slower the rate of injection (or the greater the interval between injections). This suggests (a) that the sudden death following these drugs cannot be avoided by slow injection and (b) that lethal doses of the various drugs should be compared only when the animals die within the average time of interval.

Dilution of the drug is of little value in preventing death from the intravenous injection of mercupurin.

Death is caused by action of these drugs on the heart. An early manifestation is a change in intraventricular conduction while the terminal effect is either ventricular fibrillation or respiratory failure secondary to the cardiac action.

AUTHORS.

Barker, M. H., Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics. J. A. M. A. 119: 1001, 1942.

In a search for common factors and pertinent points in four deaths following mercurial diuretics the authors note that all four patients had suffered from some

chronic wasting disease. Edema had been present in variable amounts over many months. Each patient had received diuretic salts, chiefly ammonium nitrate and potassium chloride, in variable amounts as a salt substitute. The sequence of events leading to death were similar. Three patients who had had definite cardiac damage received digitalis occasionally, but none were taking it at the time of death. One patient, however, was taking urginin. Two patients had advanced renal disease and a third had moderate cirrhosis of the liver. Three of the patients had received numerous injections of different mercurial diuretics (ranging from fifteen to two hundred) while the nephrotic patient died following the initial dose. To date the authors are unable to correlate the method of administration of the drugs, adjunct mineral diuretic salts or changes in the body chemistry with these fatalities. Because of the wasting of the body tissue, which is striking in the edematous patient, they were unable to exclude a toxic effect of a relative overdose of mercury. Whether in patients or in dogs, death by cardiac arrest is similar, regardless of the type of mercurial compound employed.

AUTHORS.

Brown, G., Friedfeld, L., Kissin, M., Modell, W., and Sussman, R. M.: Deaths Immediately Following Intravenous Administration of Mercupurin. *J. A. M. A.* 119: 1004, 1942.

In the cases of congestive heart failure the intravenous injection of 2 c.c. of mercupurin was followed by immediate death.

In 3 of the 4 cases immediate reactions were noted after intravenous injections prior to the final one. These included dyspnea, orthopnea, sweating, pallor, bradycardia, and syncope. In no case was there a delayed reaction such as might be due to massive diuresis, loss of chloride or disturbance of the electrolyte balance. In all the patients a satisfactory but not massive diuresis followed previous injections of mercupurin.

Two of the 4 patients had received intramuscular injections with adequate effect and without toxic reactions on previous occasions.

AUTHORS.

DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man. *J. A. M. A.* 119: 1006, 1942.

Mercurial diuretics are useful drugs, frequently indispensable, and it would be unwise to restrict their clinical application on account of an occasional untoward reaction. It should be borne in mind, however, that these drugs are very potent and they must be used with due consideration to contraindications, associated medication such as digitalis, state of salt and water balance, and previous reactions shown by the patient.

AUTHORS.

Corrigendum

In the November, 1942, issue of the *JOURNAL*, Vol. 24, p. 629, the article by L. N. Katz et al., in the thirteenth line, should read: . . . when QRS in lead CF₂ had only two phases of the [N] type which were not less than 3 and 5 mm., respectively, in size; when QRS in lead CF₁ had only two phases of the [N] type and the upright phase was not less than 3 mm., or when it had only one phase of the \wedge type, or when it had two phases of the \wedge type or . . .

†Inverted N.

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The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

*Executive Committee.

Original Communications

HEART DISEASE IN THE ARGENTINE*

PEDRO COSSIO, M.D.
BUENOS AIRES, S. A.

THE important and useful activity developed by United States investigators during the last few years has had great influence on the progress of medical knowledge everywhere, and the repercussions thereof in the Argentine have been so great that, today, North American medical literature predominates above that from all other countries, quite contrary to the situation in the past.

In respect to heart disease, this influence has been even more marked in my country, so much so, that the nomenclature and criteria for its diagnosis, as adopted by the American Heart Association, is used in every heart clinic, and the textbook written by the president, Paul D. White, has the greatest circulation and respect in the field of cardiology.

As a consequence, for the last few years, 90 per cent of our physicians who have gone to study abroad have chosen the United States; that is how I came to New York in 1936, and I had the good fortune to see for myself, and appreciate, that exceptionally clear-sighted man, Lewis A. Conner, whose name has been given to this special lecture on cardiovascular problems.

Now I have come again to the United States to give the Conner Lecture on heart disease in the Argentine. This quite unexpected honor is deeply appreciated by me, and should be interpreted as a generous act on the part of the American Heart Association to the investigators of heart disease in my country. This, indeed, is handsome proof of the human solidarity which binds us together more than ever in these days that challenge traditional American liberty.

PUBLIC HEALTH PROBLEMS

The Public Health Service of my country, on several occasions (Sussini and Cossio,¹ and Spangenberg²), has considered heart disease as one of the fundamental problems of public health. This is due not only

*Lewis A. Conner Lecture, American Heart Association, held in Atlantic City, N. J., June 5, 1942.

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to its wide incidence in all walks of life, but also to the gravity of the economic loss to the community.

Macera and Ruchelli³ found organic heart disease in 2.4 per cent of 10,000 school children. Bocalandro, Carrón, and Segura⁴ also found heart disease in 1.4 per cent of 6,806 soldiers who were 20 years old. Rodriguez⁵ found heart disease in 3 per cent of railway employees whose average age was 35 years. If these rates are taken in relation to the various age groups of the Argentine population, it must be accepted that, among the 13,000,000 inhabitants of my country, there are approximately 2 per cent with heart disease, that is to say, a total of 260,000 (Table I).

TABLE I
INCIDENCE OF HEART DISEASE IN THE ARGENTINE

	INCIDENCE (PER CENT)
School children	2.4
Soldiers	1.4
Railway employees	3.0

Population: 13,000,000.

Population with heart disease: 260,000.

Heart disease incidence: 2 per cent.

The official statistics of mortality show that heart disease is the chief cause of death. The average number of deaths today in my country is 161,223 per year, of which 26,068 are caused by heart disease, 24,909 by pulmonary disease exclusive of tuberculosis, 17,531 by disease of the gastrointestinal tract, 13,850 by tuberculosis, 10,813 by cancer, 10,604 by disease of the nervous system, 8,921 by infectious diseases, excluding tuberculosis, and the remaining 49,987 by various other diseases. These incidences signify the following percentages in mortality: heart disease, 16 per cent; pulmonary disease, excluding tuberculosis, 15 per cent; gastrointestinal disease, 11 per cent; tuberculosis, 9 per cent; cancer, 7 per cent; nervous system disease, 6 per cent; infectious diseases, excluding tuberculosis, 5 per cent, and other diseases, 31 per cent (Table II).

TABLE II
MORTALITY (ABSOLUTE AND PER CENT) IN THE ARGENTINE
REPUBLIC AND IN BUENOS AIRES

	ARGENTINE REPUBLIC		BUENOS AIRES	
	ABSOLUTE	PER CENT	ABSOLUTE	PER CENT
Heart disease	26,068	16	6,894	24
Cancer	10,813	7	4,286	15
Pulmonary disease, excluding tuberculosis	24,909	15	3,064	11
Tuberculosis	13,850	9	2,748	10
Disease of the nervous system	10,604	6	2,485	9
Gastrointestinal disease	17,531	11	2,273	8
Infections, excluding tuberculosis	8,921	5	1,212	4
Other causes	49,987	31	5,565	19



of age, 11 per cent among those 20 to 40 years old, and only 5 per cent in those under 20 years of age.

If this mortality from heart disease is compared to all other causes according to age groups, it will be seen that 1 in every 3 deaths is from heart disease in people over 60 years of age, and, in every 5 deaths, 1

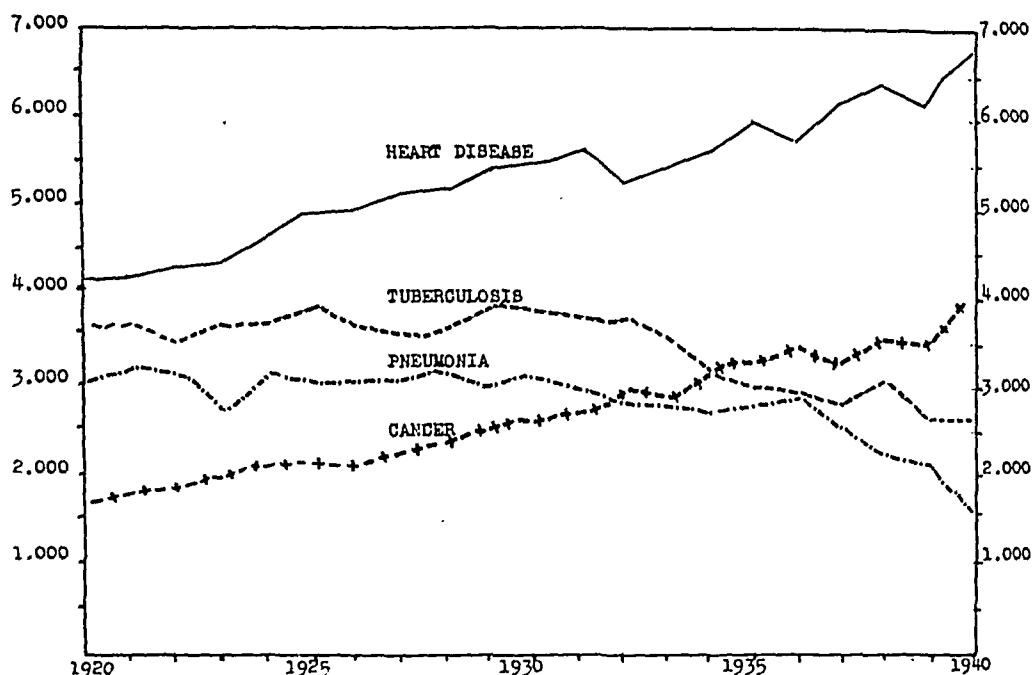


Fig. 2.—Deaths from heart disease, cancer, tuberculosis, and lobar pneumonia in Buenos Aires annually from 1920 to 1940 inclusive.

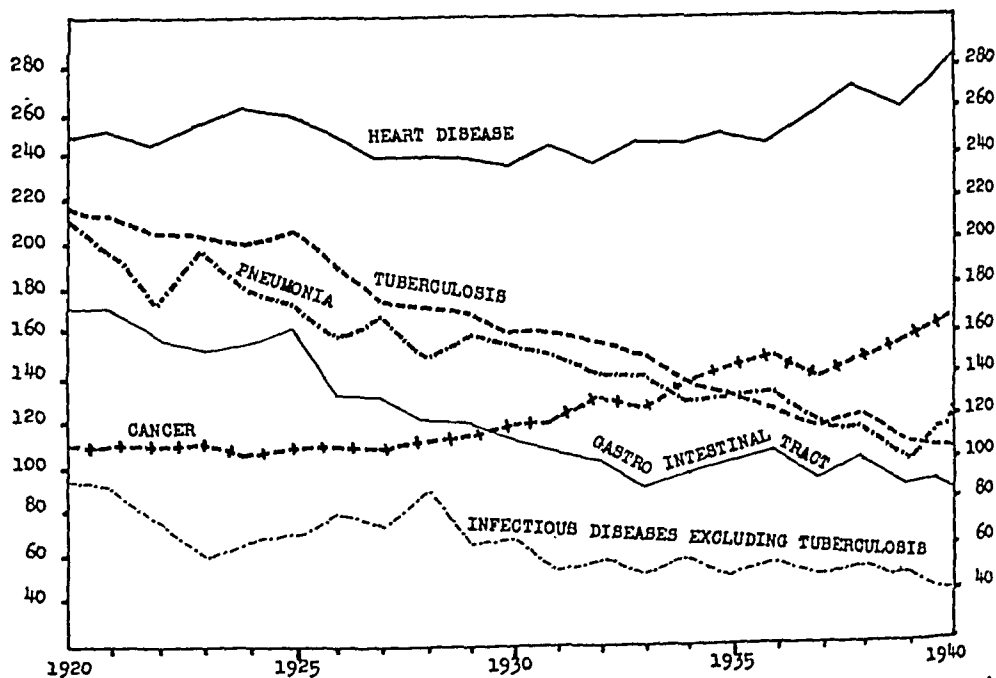


Fig. 3.—Deaths from heart disease, tuberculosis, cancer, pneumonia, gastrointestinal disease, and infectious diseases (per hundred thousand inhabitants) in Buenos Aires annually from 1920 to 1940.

is from heart disease in those between 40 and 60 years of age, whereas, in people of 20 to 40 years of age, only 1 out of 9 deaths is from heart disease, and among those under 20 years of age, 1 out of 60 is from heart disease (Fig. 1).

The predominance of heart disease in the mortality of my country has gradually become a fact during the last few years, first, by its absolute increase, and, second, as a result of lessening of some of the other causes, especially infectious diseases, including pneumonia and tuberculosis, as well as gastrointestinal diseases.

In 1920, in Buenos Aires, 4,100 persons died from heart disease (Figs. 2 and 3), which is 254 out of every 100,000 inhabitants; now the deaths number 6,894, which is 280 out of every 100,000 inhabitants.

In the same year, 1920, on the contrary, there were 214 deaths per 100,000 from tuberculosis; 213 per 100,000 from lung disease, excluding tuberculosis; 165 per 100,000 from gastrointestinal disease; and 91 per 100,000 from other infectious diseases, whereas, today, there are 110 per 100,000 from tuberculosis; 120 per 100,000 from pulmonary disease, excluding tuberculosis; 90 per 100,000 from gastrointestinal disease, and 5 per 100,000 from other infectious diseases.

It is not possible to know with any exactness the economic losses caused by heart disease, but, to give some idea, it is enough to say that 40 per cent of the pensions paid to invalids in the whole country are drawn by people with heart disease. The Civil Service Pension Board for the 300,000 government employees pays 6,000,000 Argentine paper dollars annually for heart disease incapacity alone. The Railway Pension Board for the 140,000 employees paid, during the last 18 years, 32,000,000 Argentine paper dollars for heart disease incapacity. It has been calculated that the pecuniary losses occasioned by heart disease in my country are more than 100,000,000 Argentine paper dollars per year, including medical attention and virtual salaries.

The causes of heart disease in the Argentine are the same as in other countries, but with different predominances occasioned by climate, habits, and other unknown factors.

The city of Buenos Aires, with 2,500,000 inhabitants and ways of living common to all big cities, is situated at south latitude 35°, with a temperate, but damp, climate. The causes of heart disease, according to clinical, radiologic, and electrocardiographic studies of 10,000 patients (4,000 private cases and 6,000 hospital cases, the last including more than 400 autopsies), are as follows: coronary insufficiency, 29.6 per cent; infectious disease, 28.1 per cent; rheumatism, 18.2 per cent; syphilis, 7.7 per cent; arterial hypertension, 27.5 per cent (systemic, 23.7 per cent, pulmonary, 3.7 per cent); thyrotoxicosis, 5.8 per cent; trauma, wounds, and other causes, 4.9 per cent; congenital anomalies, 2.4 per cent; and unknown causes, 1.5 per cent (Table III).

TABLE III
THE RELATIVE INCIDENCE OF THE PRINCIPAL ETIOLOGIC TYPES OF ORGANIC HEART DISEASE IN SEVERAL CITIES OF THE ARGENTINE

	CASES	CON- GENITAL (PER CENT)	RHEU- MATISM (PER CENT)	SYPHILIS (PER CENT)	CORONARY (PER CENT)	HYPERTEN- SION (PER CENT)	COR PUL- MONALE (PER CENT)	THYROID (PER CENT)	OTHER CAUSES (PER CENT)
Buenos Aires (Cosio)	10,000 (6,000 hospital and 4,000 private)	2.4	18.2	7.7	29.6	23.7	3.7	5.8	8.9
Rosario (Gonzalez Sabathic)	4,500 (3,000 hospital and 1,500 private)	2.5	18.4	9.0	20.0	36.4	1.6	3.3	8.8
Mendoza (Castro Aubone)	3,594 (3,279 hospital and 314 private)	1.5	25.0	6.8	23.0	39.6	0.9	1.2	2.0

This incidence is modified by age. Arana and Kreutzer,² in studying 1,500 children with organic heart disease, found rheumatism in 60 per cent, congenital anomalies in 28 per cent, and several other causes in 12 per cent; that is to say, of 10 children, 6 had rheumatism, 3 congenital anomalies, and 1 heart disease of another kind. Between the ages of 20 and 40 years, rheumatism remained the chief cause in 4 out of 10 cases. After 40, the most important cause is coronary disease and arterial hypertension in the following proportions: in every 10 cases there are 4 of coronary disease, 3 of hypertension, and 3 of other diseases. After the age of 60, this proportion is greater, i.e., 6 of coronary disease, 3 of hypertension, and 1 of other diseases (Cossio and Campana').

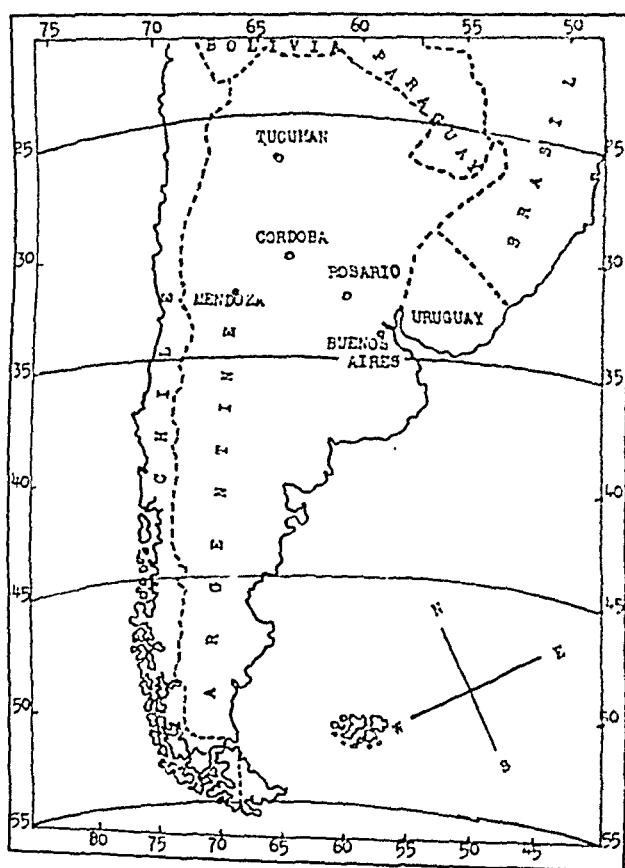


FIG. 4.

There is also a difference between private and hospital patients, depending upon their respective economic capacities. In private practice, rheumatism is slightly less frequent than among hospital patients, i.e., in the first, 17 per cent, and, in the second, 19 per cent, but, on the contrary, in private practice coronary disease, including angina pectoris, is much more common than among hospital patients; coronary disease among private patients represents 35.9 per cent, and, in the hospital group, 23.3 per cent.

It has been thought by some that a diet in which meat predominates is an important factor in atherosclerosis. Study of the causes of heart disease in the Argentine does not support this hypothesis, for the yearly consumption of meat per person is 107 kg. and the incidence of coronary disease is only 29.6, whereas, in the United States, the yearly consumption of meat per person is 66 kg. (Gomez⁸), and the incidence of coronary disease is 37.7 per cent (White and Jones⁹).

In other cities of my country (Fig. 4) the incidence of the causes of heart disease is similar to that in Buenos Aires, but with some differences according to the climate and the degree of commodities available. In Rosario, with its 500,000 people, and more or less the same climate but quieter living, Gonzalez Sabathié¹⁰ found less coronary artery disease among 4,500 private and hospital patients. Castro Aubone¹⁰ found more rheumatism among 3,594 patients in the city of Mendoza, which has a population of 83,000 but a colder winter. On the contrary, in Cordoba, with 273,000 inhabitants and a much warmer and drier climate, Maldonado Allende¹⁰ found very much less rheumatism, i.e., only 11 per cent, but more syphilis, i.e., 17 per cent.

MEDICAL TEACHING AND CARDIAC CLINICS

In 1930, Padilla and I organized, in the Physical Diagnostic Institute of the Medical School of Buenos Aires, the first postgraduate course on heart disease, which consisted of lectures and bedside teaching. Since then, other similar courses have been conducted in the Institute of Physiology and in the Ramos Mejia Hospital, also at Buenos Aires. During the last few years a postgraduate course in heart disease has been held in the Institute of Physiology of the Medical School of Cordoba. The result of these activities is that today there are in my country forty specialists in heart disease, all members of the Argentine Cardiological Society, which holds six meetings yearly in the chief hospitals of Buenos Aires. The *Argentine Heart Journal*, already in its ninth year, is the official organ of this society.

In some of the hospitals of Buenos Aires there are "cardiac clinics" and, in the others, "heart stations or laboratories" in charge of specialists in heart disease, with all the equipment necessary to make a complete diagnosis. In addition, each cardiac clinic has its own social service. The clinics have accommodations for inpatients and outpatients, the stations only for outpatients. Some cities in the interior, such as Rosario, Cordoba, Tucumán, and Mendoza, also have their own cardiac clinics or heart stations, which are organized like those in the city of Buenos Aires.

One of the cardiac clinics, for example, which is in my personal charge at the Medical School Hospital, has forty beds for cardiac patients. In addition to the regular diagnostic equipment, we have instruments for research work, such as apparatus for optical graphic and electrical

registration of heart sounds and arterial and jugular pulse, and for the estimation of cardiac output, blood and alveolar gases, blood volume, and so forth. Recently the Medical School received an important donation to endow an institution dedicated exclusively to cardiovascular investigation.

Likewise, the public health service has a department, also in my charge, for making the medical examinations that are necessary for the employees who are pensioned off for heart disease. This department also functions in the periodic health examinations of Government employees as a preventive measure against incapacity through heart disease.

RESEARCH CONTRIBUTIONS

The first original contribution in the Argentine was the syndrome happily called by Ayerza,¹¹ in 1901, "cardiacos negros," meaning black cardiacs, consisting of hypercyanosis, dyspnea, and overstrain of the right ventricle, with edema. In the beginning there was some confusion about this syndrome; it was thought to have a specific cause, and was called primary sclerosis or syphilis of the pulmonary artery (Arrillaga¹²), hyperplasia of the marrow (Escudero¹³), and so on. Later, intensive studies have shown that the initial lesion is a chronic bronchopneumonia caused by a common infection, exceptionally by syphilis or tuberculosis, with or without pulmonary arterial sclerosis and obliteration of the smaller arteries and arterioles; this is followed by overstrain of the right ventricle, with myocardial failure, which is today called chronic cor pulmonale, but with the particular characteristic that cyanosis predominates because of a disturbance in the gaseous interchange in the lungs brought about by lessening of the tension of the alveolar oxygen, i.e., so-called alveolar hypoventilation, caused by loss of the pulmonary elasticity and an increase of the pulmonary dead space (Ayerza, Solari, and Berconsky,¹⁴ Cossio and Berconsky,¹⁵ and Capdehourat¹⁶).

Several other contributions have been made, but only a few will be mentioned.

In 1917, Hardoy and Houssay¹⁷ proved, by experiments and clinical observations, the value of giving 1 or 2 mg. of epinephrine by parenteral administration in the Adams-Stokes syndrome with auriculoventricular block.

In 1921, Guglielmeti, Arrillaga, and Waldorp¹⁸ showed the effect of quinidine on the heart by experiments on dogs. After a brief phase of stimulation, with increased heart rate, a second phase of depression followed, with decreased heart rate, and lessening of the excitability of the myocardium set in, preventing or abolishing experimental fibrillation of the auricles.

In 1924, Padilla¹⁹ published a book on electrocardiography which was epoch-making in South America. Completely illustrated by his own

cases, it was an exhaustive and sound study on this important method of examination, which was quite unknown to us at that time.

Since 1928, Padilla and Cossio²⁰ have used quinidine sulfate intravenously in doses of 0.50 to 1.5 Gm. in a 5 per cent solution without harming their patients. This has been given to patients with paroxysmal tachycardia of ventricular or supraventricular origin, paroxysmal auricular fibrillation, and flutter; good results have been obtained even in cases in which this medication had been ineffective by mouth.

In 1929, Padilla and Cossio²¹ made an exhaustive clinical and anatomic study of coronary arterial occlusion, in which they pointed out the importance of alterations in auriculoventricular and ventricular conduction, and of ventricular tachycardia in cases of infarction of the interventricular septum. In addition, they demonstrated for the first time the absence of the coronary S-T segment and of the coronary T wave in myocardial infarction with bundle branch block. Battro,²² almost at the same time, made similar studies on coronary occlusion, and, some years later, Martinez²³ did the same.

In 1931, Martini and Joselevich²⁴ made an extensive clinical and anatomic study of the right ventricular failure which is caused by displacement of the interventricular septum (syndrome of Bernheim). They emphasized that the absence of lung congestion is a differential point; such congestion is characteristic of right ventricular failure secondary to left ventricular failure, which is always accompanied by pulmonary congestion of various degrees.

From 1931 until the present time, the graphic registration of heart sounds has been the object of special attention.

Braun Menéndez and Orías²⁵ have recorded the third physiologic heart sound in 42 per cent of 100 medical students, and the presystolic auricular sound in 15 per cent.

With my collaborators²⁶ I have identified a systolic and a protodiastolic sound in auriculoventricular block. The systolic sound is present when auricular contraction coincides with the middle of ventricular systole, and the protodiastolic sound occurs when auricular contraction coincides with rapid ventricular inflow, producing the summation phenomenon.

We²⁷ have given evidence of the alternation of heart sounds in cases of pulsus alternans. The alternation of the first sound and of the gallop rhythm is always concordant, whereas the alternation of the second sound may be concordant or discordant in such a way that the heart beat which produces the larger pulse wave has a loud first sound, pronounced gallop rhythm, and a loud or a faint second sound. I²⁸ have proved that often there is a third, protodiastolic sound in active rheumatic heart disease with mitral regurgitation, and also that the functional mitral murmur of rheumatic carditis occurs only in the early and middle phases of ventricular systole.

Gonzalez Sabathié²⁹ proved that, when there is physiologic reduplication of the second heart sound, the closure of the aortic valve precedes that of the pulmonary valve, which is contrary to all classical medical knowledge.

I³⁰ have shown that, with auriculoventricular nodal rhythm, the first heart sound is louder and reduplicated. This enables us to distinguish paroxysmal tachycardia of auriculoventricular nodal origin.

In 1934, Gonzalez Sabathié³¹ called our attention to engorgement of the left external jugular vein as a sign of lengthening and widening of the aortic arch, with pressure on the left innominate vein.

In 1935, Moia³² stated for the first time that the T wave of the precordial lead in normal children can be negative.

In 1937, I³³ called attention to, and named, the "bronchial dance"; this curious phenomenon, a to-and-fro movement of the bronchi on the right side, is easily seen on the fluoroscopic screen in the presence of unusual enlargement of the left auricle, with mitral regurgitation.

Also in 1937, Battro, Braun Menéndez, and Orías³⁴ showed that electrocardiographic patterns of bundle branch block are not always found with abnormal asynchronism in ventricular contraction.

In 1939, Enquin and Aguirre³⁵ were able to visualize the whole left auricle and all of the thoracic aorta by ultrapenetrating radiography, giving evidence of its usefulness in the diagnosis of heart disease.

In 1940, Arana and Kreutzer,³⁶ in a study of 600 children with diphtheria, found that the electrocardiographic changes are sometimes reversible, and, at other times, irreversible, which should be remembered in order to avoid a mistake in diagnosis.

In 1941, Vedoya and Gonzalez Videla³⁷ differentiated two types of sinoauricular block: one with occasional dropped beats and progressive lengthening of sinoauricular conduction, with heart beats in groups similar to the Wenkebach periods of auriculoventricular block; and the other, with occasional dropped beats but without the progressive lengthening of sinoauricular conduction.

Also in 1941, Cossio, del Castillo, de la Balze, and Reforzo³⁸ demonstrated reversible heart enlargement in cases of nontoxic goiter after thyroidectomy. This enlargement is apparently due to overstrain of the right ventricle caused by an arteriovenous fistula in the thyroid gland and the neighboring vascular bed.

Finally, since 1937, arterial hypertension caused by clamping the renal arteries of dogs has been the subject of a great deal of study.

In 1937, Houssay and Fasciolo³⁹ gave a clear demonstration that the ischemic kidney of hypertensive dogs liberates a pressor substance into the blood. Grafting such kidneys into the necks of recently nephrectomized dogs caused a rise in the blood pressure of the recipient dog. Later, Houssay and Taquini⁴⁰ showed that the citrated plasma of the

venous blood of ischemic kidneys produces marked vasoconstriction in the Låwen-Trendelenburg preparation of the toad.

In 1939, Braun Menéndez and Fasciolo⁴¹ showed that acute ischemia of the kidneys produced the same effects, and, with Leloir and Muñoz,⁴² discovered in this blood the substance, hypertensin, that is responsible for the pressor and vasoconstrictor properties of the venous blood of ischemic kidneys. It was found that this substance is formed by the enzymatic action of renin on a blood globulin called hypertensinogen. Another enzyme, hypertensinase, which is present in blood and tissues, destroys hypertensin. The ischemic kidneys secrete renin into the blood, and hypertensin is formed subsequently in the blood by the action of renin on hypertensinogen (Leloir, Muñoz, Braun Menéndez, and Fasciolo⁴³). Renin has been found in the renal venous blood and in the general blood of hypertensive dogs (Dell 'Oro and Braun Menéndez⁴⁴). The experiments of Huidobro and Braun Menéndez⁴⁵ have shown that renin is secreted, even by normal kidneys, whenever the blood pressure falls. The kidney thus seems to play its part in the normal regulation of arterial blood pressure.

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PATENCY OF THE DUCTUS ARTERIOSUS IN ADULTS

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THE first successful ligation of a patent ductus arteriosus was reported by Gross and Hubbard,³⁰ in 1939. Since that date, numerous additional successes, and some failures, have stimulated much interest in the subject. Gross³¹ (1941) has now operated on thirty patients with only two fatalities. The record of Jones⁴² is almost as impressive: twenty-six operations with two failures. We now have records on 134 operations to ligate the ductus; nearly half of these have not been reported except by personal correspondence to the authors. The analysis of those operations will be reported elsewhere (*Am. J. M. Sc.*, in press).

Patency of the ductus arteriosus is apparently much more common than was previously believed. We have personally studied, with some care, fifty-one patients with this condition in the Minneapolis and St. Paul area. Jones, Dolley, and Bullock¹³ have seen about sixty-five cases in the Los Angeles area. Rough calculation would suggest that there are at least 20,000 persons with a patent ductus arteriosus in the United States at the present time. There is clearly a need for careful consideration as to what should be done with these people. Apart from consideration of the immediate results of operation, there is the question as to what eventually happens to persons with patency of the ductus arteriosus in the ordinary course of events. Evidence is obtained on this point from a consideration of our own patients, many of whom have been followed for years (several for eighteen years each). In addition, there are the scattered reports in the literature which have never been satisfactorily collected and analyzed. This paper is a report on patency of the ductus in adults; adults are defined as persons 17 years of age and older. Further, we shall confine ourselves primarily to cases in which autopsies were performed. For this analysis we have clinical and post-mortem records of sixty-seven patients in the literature and four patients from our own series. Of these, sixty-one patients had no other important abnormalities and may be considered typical.

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Since this paper was written, one of our patients who had been under observation for ten years developed subacute bacterial endarteritis and was dead within three months. We were not informed of her condition until after her death. She was a sixteen-year-old girl who was apparently in good health until the endarteritis developed. Physical examination revealed typical signs of patency of the ductus arteriosus. The heart was of normal size. She had had no symptoms. Surgical treatment had been advised previously, but was refused. Post-mortem examination revealed a widely patent ductus, with superimposed bacterial endarteritis. The heart weighed 275 grams. Five additional patients have been operated upon in the past year by Dr. Owen Wangensteen, all with complete success.

Reports From the Literature.—The first case of typical patency of the ductus arteriosus in an adult, with clinical and post-mortem observations, was reported by Chevers¹⁷ in 1845. The patient, an adult woman, was said to have died of tuberculosis, but, from the meager history and post-mortem report, it appears possible that death may actually have been caused by subacute bacterial endarteritis.

Brief notes on the cases from the literature are given in Appendix A to this article. Before considering the salient characteristics of these cases, we shall report the adult patients of our own who came to autopsy.

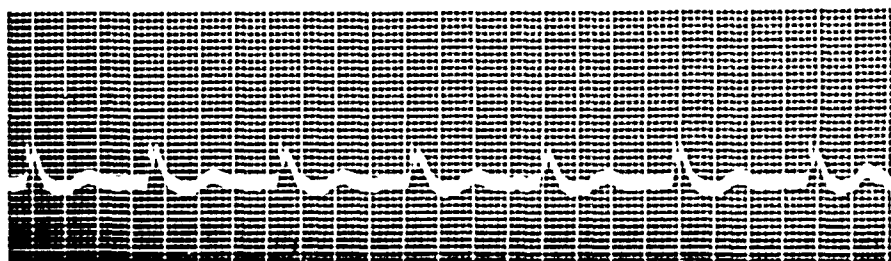


FIGURE 1a

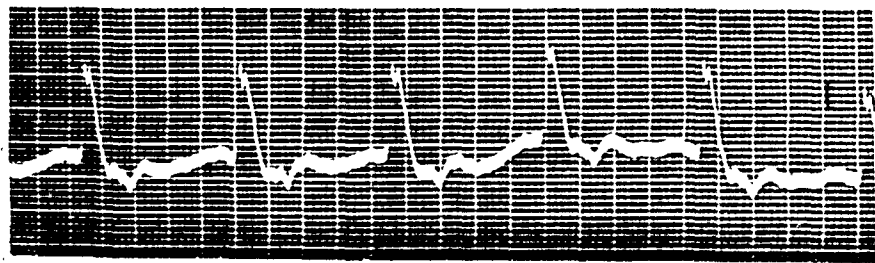


FIGURE 1b

Fig. 1a.—Stethocardiogram and simultaneous pulse wave record on patient No. 1, before operation. Stethophone in second left intercostal space, pulse recorder on right brachial artery.

Fig. 1b.—Same as Fig. 1a, but four days after operation. Note that same amplification was used as in Fig. 1a.

REPORT OF AUTHORS' CASES

In a total of 51 cases, we have had 4 adult patients who came to autopsy. These are as follows:

CASE 1.—This 18-year-old man had been studied repeatedly over a period of 6 years; the diagnosis of heart disease had been made at the age of 2 years. His

general health had been fairly good, but there was an increasing complaint of exertional dyspnea, cough, and inability to do physical work. At the same time there was a gradual increase in the blood pressure, the size of the heart shadow, and the density of the hilar shadows. Surgical closure of the ductus was recommended. At operation the posterior junction of the ductus and pulmonary artery was ruptured, and the bleeding could be controlled only by clamps. The patient died on the ninth postoperative day.

Physical Examination Before Operation.—The patient was well developed and nourished, with no cyanosis, clubbing, or signs of cardiac failure. There was a marked thrill over the pulmonic area, and, in this region, there was a loud murmur which was typical of patency of the ductus arteriosus; the murmur was transmitted upward, to the left, and to the back. The heart was moderately enlarged, chiefly to the left. The apical impulse was visible in the sixth left intercostal space. The pulmonary arc was considerably enlarged. The blood pressure was 144/40, and the pulse rate, 88. There were a Corrigan pulse in the neck and a capillary pulse in the finger tips.



Fig. 2.—Roentgenogram of chest of patient No. 1 after operation. Note clamps on ductus and adjacent portion of pulmonary artery.

Special Examinations.—On 3 occasions, in the basal resting state, the blood pressure in the right arm was 152/40/0; in the left arm, 146/60/0; in the right leg, 204/120/80/0; in the left leg, 190/60/0; the pulse rate was 84. The basal metabolic rate was +1 per cent, -2 per cent. Total systolic heart volume (roentgenkymograph) was 980 c.c. Total body surface, 1.75 M². Net cardiac output (acetylene), 3.79 L./min., stroke, 43.8 c.c. Gross cardiac output (roentgenkymogram), 7.56 L./min., stroke, 90 c.c. Flow through ductus, about 50 per cent of output of left ventricle.

Autopsy (abstract).—Body length, 179 cm.; weight, 145 pounds. Moderate cyanosis of nailbeds; no jaundice. Left lung collapsed, left pleural cavity filled with fibrinoplastic material with numerous pockets of clear serous fluid. There were about 50 c.c. of this fluid in the right pleural cavity.

About 150 c.c. of slightly bloodtinged purulent fluid were found in the pericardial cavity. A fine, plastic, readily broken exudate united the pericardium with the anterior surface of the left ventricle. *Streptococcus viridans* was cultured from the pericardial material. There were five hysterectomy clamps in the region of the ductus arteriosus.

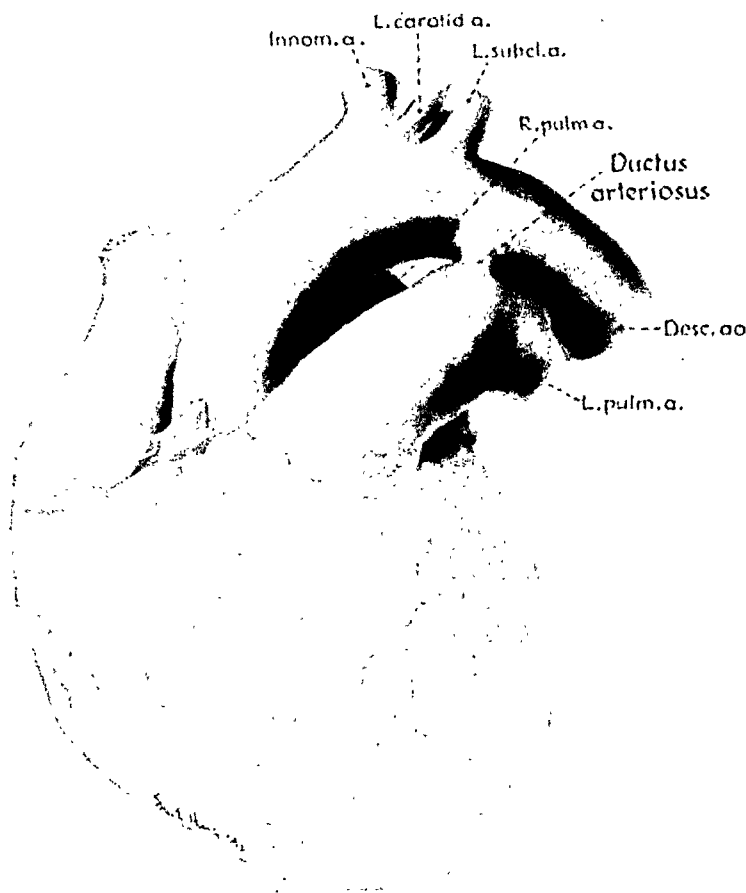


Fig. 3.—Anterior view of the heart and great vessels of patient No. 2.

Heart weight, 650 grams; generalized hypertrophy, more on right than the left side. Marked right-sided cardiac dilatation. All valves and chambers normal; marked hypertrophy of the papillary muscles of tricuspid and mitral valves. Length of the ductus arteriosus, 5 mm. on the cardiac side, and 2 or 3 mm. on the lateral side. The aortic orifice was about 8 mm. in diameter, the pulmonary orifice, 3 mm. Minimal atherosclerosis in the aorta, none in the pulmonary artery.

The left lung was completely atelectatic, with no emboli, infarcts, or abscesses. The upper lobe of the right lung showed moderate edema; most of the lower right lobe was atelectatic. There was a sterile abscess, 2 cm. in diameter, in the head of the pancreas. There was nothing else of importance.

Diagnoses.—(1) Patency of the ductus arteriosus, (2) surgical closure of the ductus, (3) atelectasis of left lung, (4) slight fibrinous pericarditis, and (5) fat necrosis of the pancreas.

Comment.—The attempted ligation of the ductus was justified in view of the evidence of decreasing tolerance to the condition. The shortness of the ductus on one side presented a difficult surgical condition. After the ductus was clamped off, the patient's condition was fair, and the blood pressure was 125/80. Nine days later, at death, there were no signs of union of the compressed inner surfaces of the ductus.

CASE 2.—This 58-year-old man was admitted to the hospital with complaints of stomach trouble for many years, and weakness, with gastrointestinal symptoms, for 18 months. A diagnosis of carcinoma of the stomach was followed by subtotal gastrectomy. Death occurred 38 days later, preceded by pulmonary edema and hydropneumothorax.

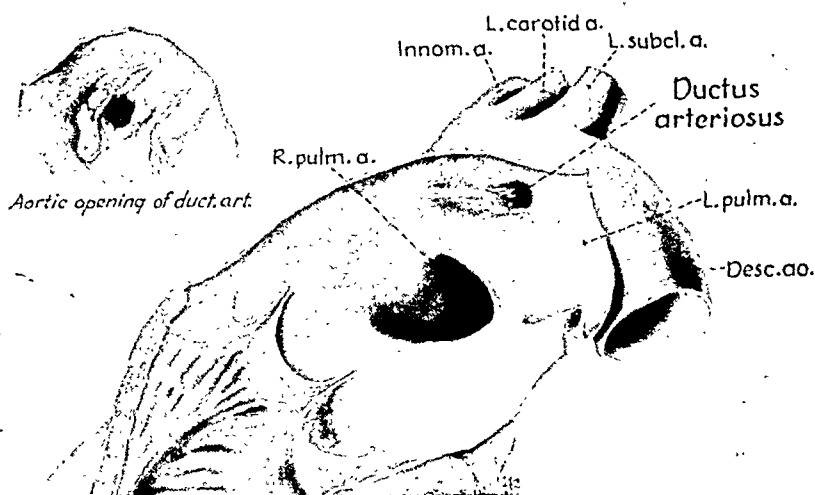


Fig. 4.—Opened aorta and pulmonary artery of patient No. 2. Note normal pulmonary endothelium, with atheromatous patch at the orifice of the ductus.

History.—Aside from the long history of stomach trouble and a transurethral prostatic resection 6 years before admission, this patient had always been reasonably well and able to earn a living at fairly hard work. Twenty years earlier he had been told he had heart trouble but had suffered no symptoms except moderate exertional dyspnea. A diagnosis of patency of the ductus arteriosus was made prior to gastrectomy.

Physical Examination.—There was a machinery murmur, typical of patency of the ductus arteriosus, with a slight thrill, over the pulmonic area. The heart was enlarged to the left; the pulmonary artery was prominent; the aorta was somewhat tortuous and calcification was present in the arch. There were no signs of cardiac failure. The blood pressure was 126/56.

Special Examination.—The blood pressure in the right arm was 130/58; in the left arm, 154/58; in the right leg, 160/60; and in the left leg, 160/60; pulse rate, 94. Total body surface, 1.70 M². Basal metabolic rate, +35 per cent; +22 per cent. Total systolic heart volume (roentgenkymogram), 660 c.c. Gross cardiac output (roentgenkymogram), 5.76 L./min.; stroke, 62 c.c. Flow through ductus, about 30 per cent of total left ventricular output.

Autopsy (Abstract).—Body length, 180 cm.; weight, 140 pounds. No jaundice or cyanosis; slight edema of the ankles. Atelectasis and crepitation of the lungs, three large decubital ulcers on the back, marked dilatation of the large bowel.

The heart (and great vessels) weighed 550 grams, and both ventricles were hypertrophied. The ductus arteriosus was very short, but widely patent. The chambers, myocardium, and valves were normal. The pulmonary conus was dilated; the intima of the pulmonary artery was smooth and normal except for thickening in the region of the orifice of the ductus. The aortic wall showed moderate calcification in this region but was otherwise normal. Atherosclerotic changes were generally absent in the great vessels and were minimal in the coronaries.

The liver weighed 1,850 grams, and showed pigmentation, congestion, and central atrophy.

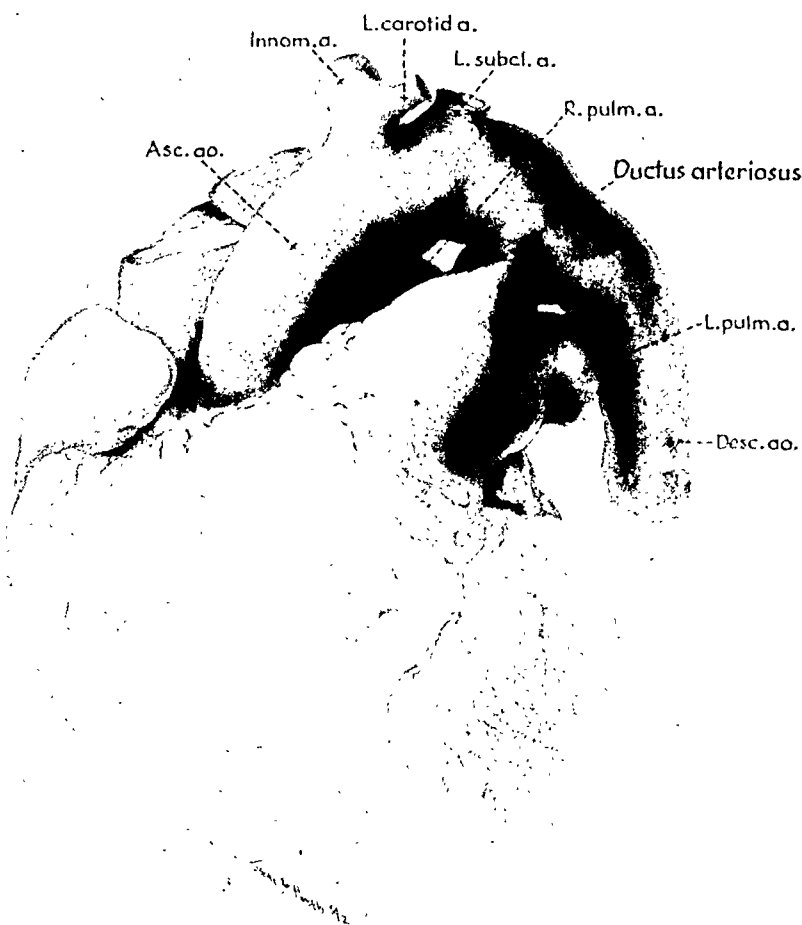


Fig. 5.—Anterior view of the heart and great vessels of patient No. 3.

Diagnoses (Abstract).—(1) Carcinoma of the stomach, removed surgically, (2) hydrothorax, (3) pulmonary edema, (4) paralytic ileus (colon), (5) patency of the ductus arteriosus, (6) cardiac hypertrophy and dilatation, and (7) chronic passive congestion of liver.

Comment.—This patient had suffered remarkably little disability from patency of his ductus arteriosus throughout a life of moderately hard physical labor. There is no reason to believe that his death was related to the cardiac condition. Ligation of the ductus would have been difficult because of its shortness. The normal condition of the intima of the pulmonary artery was notable.

CASE 3.—This 46-year-old woman was admitted to the hospital July 29, 1941, and died August 7. Her entering complaints were dyspnea, nausea and vomiting, anorexia, and pains in the feet, all of which had gradually increased in severity for several weeks.

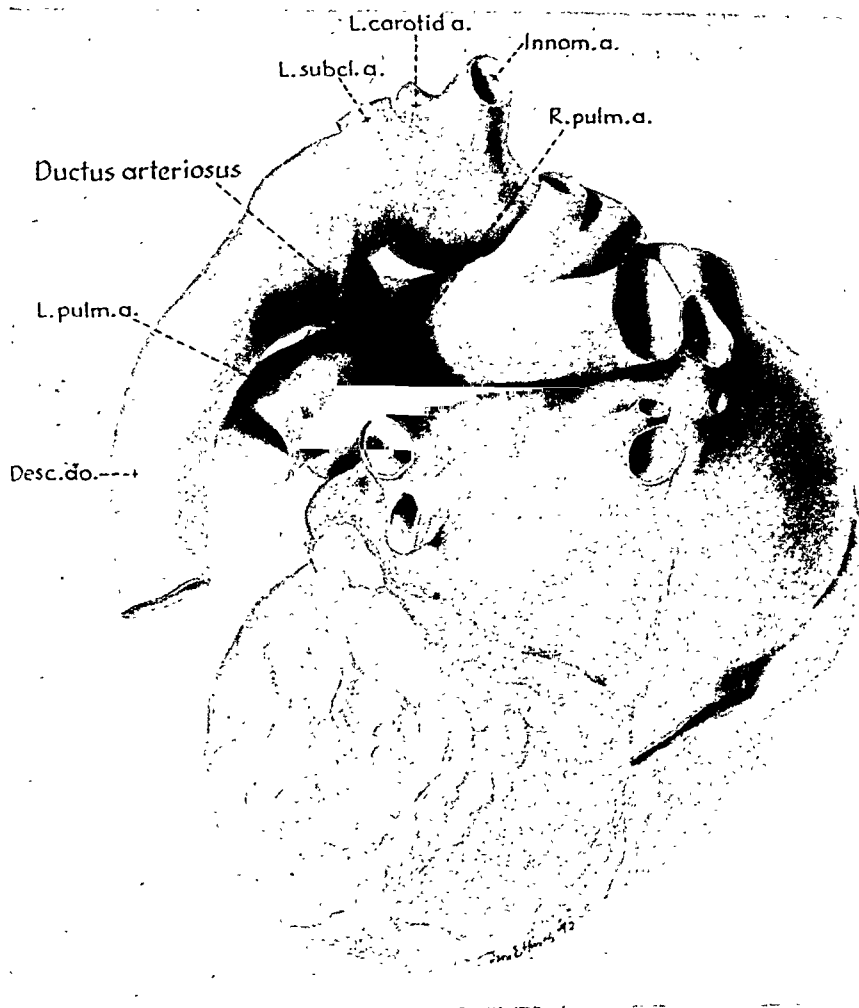


Fig. 6.—Posterior view of the heart and great vessels of patient No. 3.

History.—Since the age of 5 years, she had known that she had heart trouble, and had always led a somewhat sheltered but otherwise normal life. Her general medical and family history were unimportant.

Physical Examination.—She was well developed and moderately obese. There were generalized anasarca, moderate ascites, and moderate cyanosis. The heart was greatly enlarged to the right and left, and the contour was that of congenital or mitral disease. The pulmonary artery was markedly enlarged, and the hilar shadows much enlarged. The heart sounds were rapid and regular, with no murmurs; there were râles in both bases. There was no fever or petechiae. The blood pressure was 142/40.

Urinalysis.—Sp. gr., 1,030; albumin, +++; occasional bacteria and 6 to 8 leucocytes per microscopic field.

Diagnosis.—Congestive heart failure and congenital heart disease (interauricular septal defect?).

Course.—The patient grew worse rapidly and died of heart failure.

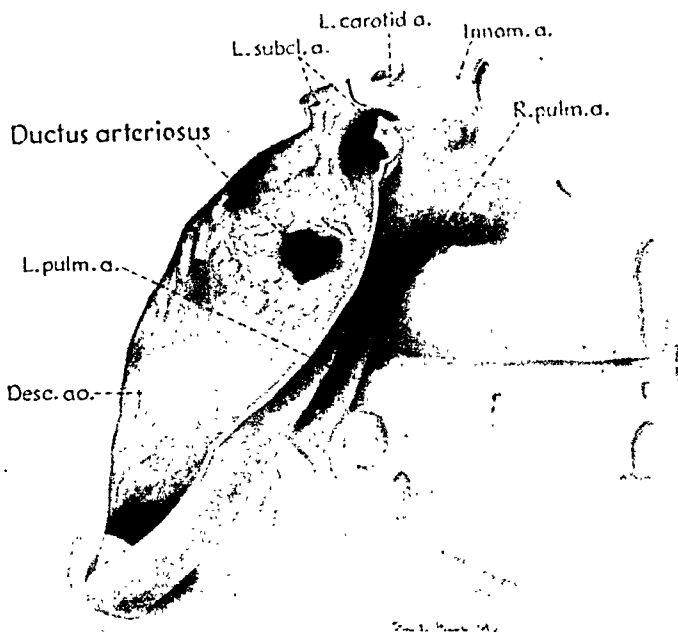


Fig. 7.—Opened aorta of patient No. 3. Note numerous atheromata and slight fold at orifice of the ductus.

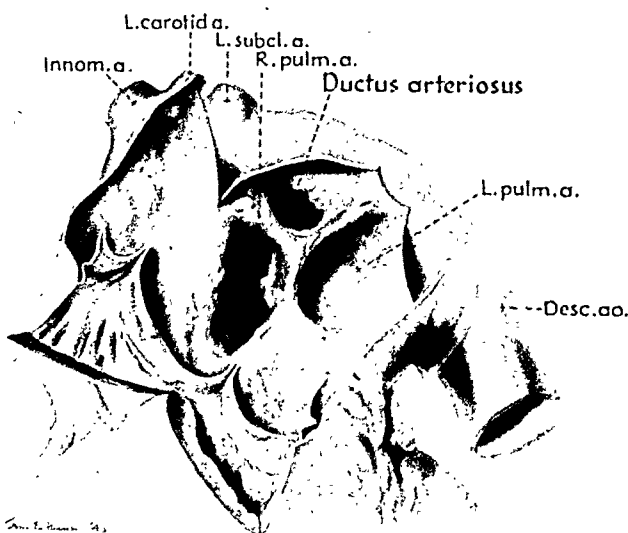


Fig. 8.—Opened pulmonary artery of patient No. 2. Note atheromata.

Autopsy (Abstract).—No edema, cyanosis, or jaundice. Weight, 125 pounds; length, 157.5 cm. The liver extended 6 cm. below the xiphoid and 2 cm. below the costal margin.

The heart weighed 700 Gm.; it showed marked right ventricular hypertrophy and some left ventricular hypertrophy. The ductus arteriosus was patent and was about 2 cm. long and 1.5 cm. wide. The pulmonary conus and the branches of the pulmonary artery were markedly enlarged. All of the valves were normal, and there were no septal defects. There was minimal atherosclerosis of the coronary arteries; the coronary orifices were normal. There was marked intimal atherosclerosis of the root of the aorta, the ductus arteriosus, and the pulmonary artery.

The liver weighed 1,425 Gm. and showed moderate congestion.

Microscopic examination revealed marked arteriosclerosis of all branches of the pulmonary artery. There was a large ante-mortem clot in the right main branch of the pulmonary artery.

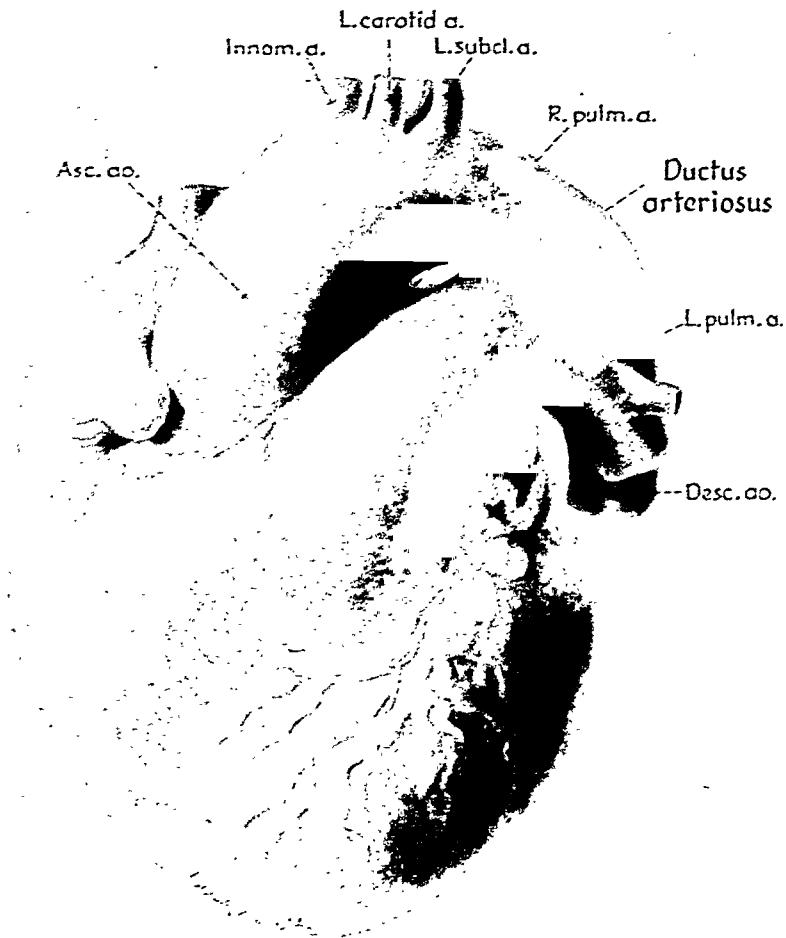


Fig. 3.—Anterior view of heart and great vessels of patient No. 4.

Diagnoses.—(1) Patency of the ductus arteriosus, (2) right ventricular hypertrophy and dilatation, (3) pulmonary thrombosis or embolism, (4) pulmonary arteriosclerosis, and (5) mild chronic passive congestion of the liver.

Comment.—The large patency of the ductus arteriosus allowed 46 years of moderately normal life but ultimately led to right ventricular failure. The diagnosis was impossible because there was no murmur. It is possible that the murmur was audible before the onset of failure. Anatomically, there appeared to be no reason why ligation could not have been performed successfully.

CASE 4.—This 53-year-old woman was first admitted to the hospital September 2, 1941, and died February 5, 1942. Her entering complaints were headaches, nausea, vomiting, and fever, beginning about August 27, 1941.

History.—She had been told her heart disease was discovered before she was one year of age. A definite diagnosis of congenital heart disease was made at the age of 12 years. She had never been incapacitated but was always forced to restrict her physical activity. At no time did she have complaints suggesting cardiac failure. At the age of 19 she had received digitalis for a time (reason unknown).

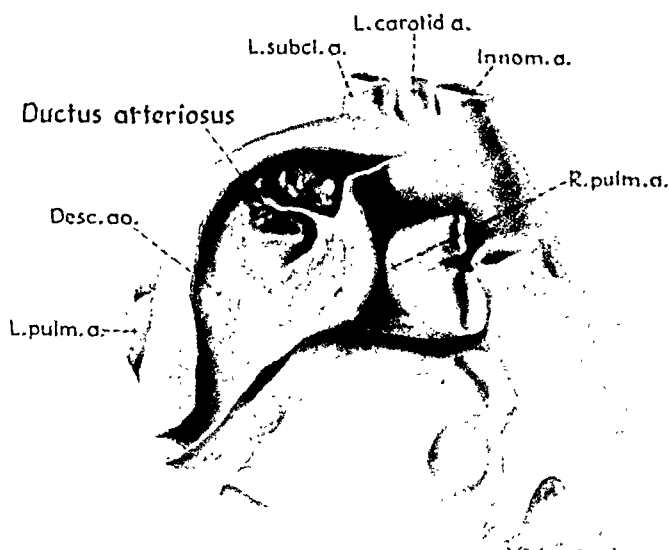


Fig. 10.—Opened aorta of patient No. 4. Note atheromata and fold at orifice of ductus.

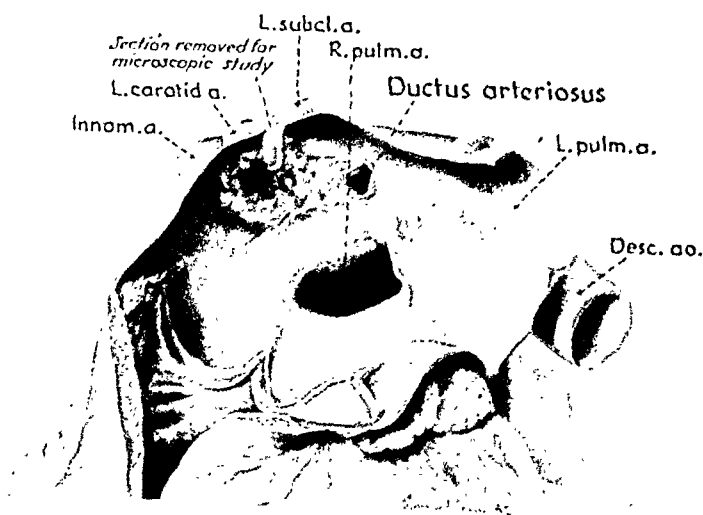


Fig. 11.—Opened pulmonary artery of patient No. 4. Note heavy patch of atheromata.

Physical Examination.—She was well developed and nourished. There was no cyanosis or clubbing. A systolic thrill was palpable in the second left intercostal space, and a machinery murmur, typical of patency of the ductus arteriosus, was heard over this region. The systolic phase of the murmur was transmitted upwards and to

the back. She had a Corrigan pulse and a capillary pulse in the finger tips. There were râles in both bases. Both the liver and spleen were palpable, but not tender. There were no petechiae. The blood pressure in the arm was 140/65, and in the leg, 170/96. Her temperature ranged from 98° to 103° F. *Streptococcus viridans* was recovered from the blood culture in 48 hours. The hemoglobin was 74 to 80 per cent.

The heart was enlarged to the left and right. There were marked enlargement of the pulmonary artery and increased shadows of hilar vessels.

Urinalysis.—Trace of albumin; sp. gr., 1.002 to 1.018; no casts or erythrocytes; 1 to 8 leucocytes.

Diagnosis.—Patency of the ductus arteriosus, with superimposed subacute bacterial endarteritis.

Course.—Several courses of sulfathiazole, sulfanilamide, and sulfadiazine were ineffective. Repeated blood transfusions increased the hemoglobin level from 55 per cent to 89 per cent. The temperature was normal during the last three weeks in hospital. Arrangements were made to attempt to ligate the ductus, but the patient expired after twenty minutes of anesthesia (cyclopropane intratracheally) before the operation was started.

Autopsy (Abstract).—No edema, petechiae, or jaundice; marked cyanosis. Body length 158 cm.; weight, 110 pounds. The liver was 11 cm. below the xiphoid process in the midline, but even with the costal margins on the right and left.

The heart weighed 490 Gm.; it showed slight hypertrophy of the right ventricle and more marked hypertrophy of the left ventricle. The aortic, pulmonary, and tricuspid valves were normal. The mitral valve showed some old thickening and two recent vegetations on the medial leaflet. The coronary orifices were normal. The ductus arteriosus was patent and measured 12 mm. in external diameter; its smallest bore was about 3 mm. in the contracted specimen. Vegetations and several atheromata were present in the pulmonary artery. There was an infarct, 1 cm. in diameter, in the upper lobe of the left lung, and another, 3 cm. in diameter, in the left lower lobe. The spleen was firm, deep red in section, and weighed 520 grams. The liver showed long-standing passive congestion, and weighed 1,720 grams.

Diagnoses.—(1) Subacute bacterial endarteritis, (2) patency of the ductus arteriosus, (3) infarcts of lung, (4) ascites, (5) chronic passive congestion of liver, (6) septic splenitis, (7) uterine myomata, (8) left ventricular hypertrophy, and (9) dilatation of left auricle and ventricle.

Comment.—The correct diagnosis was not made by the original attending physician. The physical condition of the patient at this time, some months after the onset of the infection, made her a poor operative risk.

ANALYSIS OF 60 CASES IN ADULTS

In an analysis of pathologic changes and cause of death it is not justifiable to include our own Case 1, so that we have in our series a total of 60 adults with typical, simple patency of the ductus. There were 14 men and 46 women; 76.7 per cent were women. The preponderance of females with patency of the ductus arteriosus is, if anything, more marked in adults than it is in series of all ages and of children previously summarized in the literature. For example, in Maude Abbott's² series of 97 cases in which the average age was 21.2 years at death, the females comprised 63 per cent of the total.

The average age at death of the 14 men in the present series was 38.9 years; that of the 46 women was 35.5 years. The oldest man died at 58, and the oldest woman, at 66 years. We can estimate the reduction in

length of life by comparison with the average life expectancy of the general population. Properly, this comparison should be made for each individual in this series, using the life tables for the year of death and for the country of residence. Such exact comparison is impossible, but a reasonable estimate can be made. Since the life expectancy of adults is not greatly different in the United States, England, and the northern European countries in which the rest of the patients resided, we can refer to the United States Life Tables with no great error. Further, the life expectancy of adults has shown a fairly constant, slow increase in these countries for many years. The chronological mid-point of the present series is close to 1910; that is, roughly, half of the patients died previous to that time. Accordingly, it appears desirable to use the tables for that year.

By this means we can say that the presence of patency of the ductus arteriosus in the persons in the present series coincided with an average reduction in life expectancy of about 23 years in the men and 28 years in the women. Expressed in another way, we can say that these people, who were alive at the age of 17, had a life expectancy which averaged about half that of the population as a whole. The interpretation of these figures will be treated further in the Discussion.

The cause of death in these cases is shown in Table I. Subacute bacterial endarteritis accounted for more than 40 per cent, and congestive heart failure for nearly 30 per cent. The two deaths from rupture of aneurysms of the pulmonary artery (Nos. 26 and 41) also must surely be ascribed to the condition of the ductus. Roughly, 4 out of 5 of these persons eventually succumbed to the effects of patency of the ductus. This is the more striking when we note that the majority of these persons lived many years, during which they were apparently well adjusted to the defect.

TABLE I

CAUSE OF DEATH IN 60 ADULTS WITH PATENCY OF THE DUCTUS ARTERIOSUS

NO.	%	CAUSE	NO.	%	CAUSE
25	41.7	Subacute bact. end-art.	2	3.3	Prob. subacute bact. endart.
17	28.3	Cong. failure	3	5	Tuberculosis
2	3.3	Rupt. pulm. aneurysm	2	3.3	Rupt. aortic aneurysm
2	3.3	Cerebrovascular	1	1.7	Pneumonia
1	1.7	Ca. of stomach	1	1.7	Yellow atrophy
1	1.7	Suicide	3	5	Questionable

It is generally stated that hypertrophy of the right side of the heart is characteristic of patency of the ductus arteriosus, and this is said to be the result of increased pressure in the pulmonary artery. Table II summarizes the observations in the present series. It is clear that hypertrophy of the right side of the heart is frequent, but, in many cases both sides were equally hypertrophied, and cases of predominantly left-sided heart hypertrophy are not rare. In some cases neither side was hypertrophied.

TABLE II
THE SIZE OF THE HEART IN 60 ADULTS WITH SIMPLE PATENCY OF THE
DUCTUS ARTERIOSUS

ENLARGEMENT	PREDOM. RIGHT	PREDOM. LEFT.	BOTH SIDES
Great	11	2	4
Moderate	8	4	10
Slight	2	2	3
No enlargement		5 cases	
Not stated		9 cases	

Dilatation of the pulmonary artery is, of course, frequently associated with patency of the ductus arteriosus. It is not uncommon, however, to find that such dilatation is not demonstrable roentgenologically. We believe that this dilatation is, in fact, nearly always present in adults, for it occurred in the majority of the patients in the present series. In ten cases, actual aneurysms of the pulmonary artery were present. There may be some argument as to the definition of "aneurysm"; certainly many fusiform dilatations of the pulmonary artery do not merit the term. When the dilatation is profound and well circumscribed, however, with degenerative changes in the walls, such an appellation seems justified. We have noted that spontaneous rupture of such aneurysms resulted in two deaths.

The presence of atheromata and calcareous plaques in the pulmonary artery has been noted many times before and was prominent in all of our cases (cf. Figs. 4, 8, 11). This is so frequent that it is the rule in adults. Exceptions occur, however, notably the 65-year-old patient of White.⁹¹ The fact that these atheromata and plaques occur with almost equal frequency in the aortas of these patients has not been stressed previously.

The length of the ductus is of interest in view of the present possibilities of ligation. In general, the ductus is short in adults, and cases in which it is a centimeter or more in length are rather rare (Appendix A, Nos. 24, 27, 40, 46, 52, 53). Cases are not uncommon in which the ductus is extremely short, or even reduced to a mere fistula-like opening between the aorta and pulmonary artery. In the present series, cases of this type, representing very difficult or frankly inoperable conditions, comprised 17 per cent of the total (10 out of 60 cases, cf. Appendix A, cases 2, 4, 10, 18, 19, 25, 33, 37, 48, 55). Lenz⁵³ reported a case of this type in an adult, with calcification of the point of junction of the aorta and pulmonary artery; we have been unable to obtain the paper in which this is reported, so that we have not included the case in the present series. The frequency of this condition appears to be considerably greater in adults than in infants and children, although it may occur in very young infants (Lediberder⁵²).

It would be of much interest to compare the size of the lumen of the ductus with the severity of the cardiac disability and cause of death in these cases, but this is not possible because of the absence of quanti-

tative data on the bore of the ductus. Even if post-mortem measurements were available, accurate comparison would be difficult because of the fact that the size of the bore in the post-mortem contracted specimen may be quite different from what it was in life, when the vessel was distended with blood under arterial pressure. We might expect that congestive failure would be more frequent when the communication is very large, but no real proof of this exists.

The diagnostic signs in the present series clearly pointed to patency of the ductus arteriosus in most of the cases, and, except in the earlier cases, the diagnosis was made correctly in the majority of instances. In several instances, however, the diagnosis could not be made because there was no murmur. This was true in the case of Duroziez²² and in one of our own cases (Case 1). Foulis²⁵ found that the murmur in his case disappeared entirely twenty-six days before death. All of these three patients died of congestive failure. The history in Motzfeldt's⁶¹ first case (Appendix A, No. 31) was incomplete, but the diagnosis was not made, and it is explicitly stated that there was no mention of any murmur. In addition, in two instances only faint atypical murmurs were heard (Appendix A, Nos. 36, 39).

Sternberg⁷⁵ stated that there is always a characteristic shape and form of the patent ductus arteriosus, in that the opening of the ductus into the aorta is funnel-shaped, and at the pulmonary orifice there is some sign of a membrane or ridge. Jores⁴³ agreed that this condition is very frequent, but also recognized several other types: (1) Extreme shortening, (2) aneurysmal ductus, and (3) cylindrical ductus. In the present series we have already noted the extremely short ductus type. Cases in which the aortic orifice of the ductus was considerably larger than the pulmonary orifice are frequent (Appendix A, Nos. 12, 17, 22, 23, 27, 29, 30, 36, 37, 39, 46, 53). In at least one case, however, the pulmonary orifice was larger than the aortic orifice (Appendix A, No. 24). The membrane or ridge referred to by Sternberg has been extensively discussed since Strassmann's⁷⁷ publication of his theory of closure. In adults, at least, such a condition is occasionally seen (Wells;⁹⁰ cf. Figs. 7 and 10), but does not appear to have any important significance; a fold of the wall may occur at both orifices,⁵⁴ but tends to occur at the aortic orifice because of the acute angle of insertion of the ductus into the aorta (cf. Roeder⁶⁸).

COMPLICATED AND ATYPICAL PATENCY OF THE DUCTUS

Patency of the ductus arteriosus is peculiar among congenital defects in that it so frequently occurs without associated abnormalities. In Maude Abbott's² series of 1,000 cases of congenital heart disease at all ages, simple patency of the ductus occurred in 92 instances, and, in 150 instances, patency of the ductus complicated other defects. Most of the latter patients died in infancy or at an early age, and we suspect that

the relative proportion of simple patency to complicated conditions is considerably greater in adults.

We have collected data on ten adults, with post-mortem observations, in whom patency of the ductus was the most prominent abnormality, but in whom the patency was not typical or some other defect was present. These are listed, with brief notes, in Appendix B of this paper. This list could be easily enlarged by including cases of transposition of the great vessels, septal defects, pulmonary atresia, and so on, but these have been excluded in the belief that it is not a concern of this inquiry to examine situations in which patency of the ductus is secondary to other defects.

It is of interest to note that, in this series, nine of ten of the patients were men. In four instances there was associated coarctation of the aorta (Appendix B, Nos. 1, 3, 8, and 9). In three instances the ductus was aneurysmal and filled with an organized or partly organized clot (Nos. 2, 6, 10). The experience of Graham²⁵ is illuminating. He tried to remove a mediastinal tumor and discovered, post mortem, that the tumor was in reality an aneurysm of the ductus arteriosus. Shortly afterward he encountered a similar case surgically, but was able to retreat before it was too late.

The two cases reported by Wagener²⁶ are curiosities. In each instance the ductus was open to the pulmonary artery, but the orifice of the latter was closed by a firm membrane. This membrane was pierced by a single pinhole in one patient and by two such pinholes in the other. As one would expect, there was no cardiac disability in either case.

DISCUSSION

The application of autopsy results to clinical prognostication is always difficult because of the question of selection of cases. This was recognized by Bullock, Jones, and Dolley,¹⁴ who included many of the present cases in their discussion of cause of death in patency of the ductus arteriosus. Specifically, the chief possibilities that the present series is not representative seem to be: (1) Remarkable and peculiar cases tend to be reported more frequently than typical cases. (2) Patency of the ductus may be unrecognized and therefore unreported, when patients die of noncardiac conditions.

With regard to the first point, it will be agreed that remarkable cases are more frequently reported. Patency of the ductus in the adult is and has been generally considered a rather remarkable abnormality, regardless of the cause of death. If anything, we should expect that authors would compete to report the oldest patients and those cases in which a marked lesion was well tolerated. In other words, we might believe that the present series would include the oldest patients, as well as those cases in which the cardiac lesion had no relation to death. If this were true, the analysis of the present series would underestimate the disabling and lethal effect of patency of the ductus.

It is certain that many autopsies on persons with patency of the ductus fail to disclose the lesion because of the frequent use of the method of removing the heart in which the aorta and pulmonary artery are severed proximal to the ductus. This error would tend to be more frequent in cases of noncardiac death, and hence there would be a tendency to overestimate the disabling and lethal effect of patency of the ductus.

One important question may be asked: Where are the adult, living patients with patency of the ductus? In any large city it is possible to find a few cases of patency of the ductus, but, in our experience, these are almost always in children. Further, it should be emphasized that, when we are dealing with adults, at least, there is no reason why persons with patency of the ductus who die in the second and third decades should be discovered more readily or reported more often than those who die later.

Many of the patients in our own clinical series have been observed for years, and fully half of them for periods of four to eighteen years. With the exception of the patient who died after operation, only one of them exhibited any very marked change of status during all this time. (In Cases 3 and 4 in the series presented in this paper the patients were not seen prior to the beginning of the final illness.) In general, they live fairly normal lives, go to school, or earn a living. One patient, a man of 35 years, is a playground supervisor. Another patient, a woman of 19 years, wishes to study physical education in the University. A third patient, a man of 28 years, has been rejected by the Army but works steadily at heavy manual work and has remarkable muscular development. Among the adults, only one, a prostitute of 31 years, shows signs of impending, serious, cardiac embarrassment.

These facts could be taken as evidence that most patients with patency of the ductus arteriosus need not have the ductus ligated. Our patients are still quite young, however, and the fact that they keep in excellent condition, even for a good many years, does not mean that they have any security against eventual subacute bacterial endarteritis or cardiac failure. It is striking in our own experience, and in the cases listed in Appendix A, that patients with patency of the ductus arteriosus do not, in general, have long and repeated periods of failure or great cardiac disability before the final illness. Almost none of them are "cardiac cripples." It is the rule that they maintain good compensation until either subacute bacterial endarteritis or cardiac failure intervenes. Very few survive once they develop failure; in this respect, these patients are in marked contrast to patients with mitral disease. Subacute bacterial endarteritis is just as fatal in cases of patency of the ductus arteriosus as in other types. There is a record of one case in which a patient with a patent ductus developed subacute bacterial endarteritis and finally recovered completely after several years;¹⁶ the treatment in this case was entirely symptomatic.

The diagnosis of patency of the ductus arteriosus can be made with great certainty, as shown by the fact that we know of only two diagnostic errors among 134 patients who were operated upon. We should note that, in general, patients about whom there is any question of diagnosis will not be subjected to surgical exploration. Certainly we know, as was observed earlier in this paper, that anatomically typical patency of the ductus can exist with only an entirely atypical systolic murmur or even with no murmur at all. Those conditions seem to occur most frequently in the final stages of failure and may represent only a terminal abnormality of blood pressure relationships in the great vessels.

Very rarely it may happen that a murmur and other signs typical of patency of the ductus arteriosus will exist for years and then disappear, leaving the patient apparently normal. We have had two cases of this type, and several others, not very well authenticated, have been recorded in the older literature. We are discussing these apparently spontaneous closures elsewhere, but here it is enough to indicate that the phenomenon may occur, but is certainly very rare, and probably need not be considered in any practical analysis of the eventual outlook for patients with patency of the ductus.

The natural history of patency of the ductus in the adult indicates a prognosis that is good to the extent that the patient may usually expect to live a considerable number of years with relatively slight disability. On the other hand, every patient is faced with the constant threat of subacute bacterial endarteritis. Moreover, we can at best do no better than say that life will probably be short. As far as can be seen, there is no reason to place these patients on any particularly restricted regime; patients who are voluntarily quite active seem to get along as well as the patients who are constantly prevented from the slightest exertion.

The present discussion can hardly close without some statement as to the desirability of ligation of the ductus. Elsewhere we shall present an analysis of 134 operations; the salient features are low mortality and a high percentage of what seem to be complete cures. Such patients should be freed of the possibility of developing congestive failure. It is not yet certain that these patients are completely insured against subacute bacterial endarteritis. In adults, at least, it is probable that there are some atheromata in the great vessels, and these might present focal points for infection. We cannot say whether these atheromata will eventually regress. In any event, the orifices of the ductus in the aorta and the pulmonary artery will represent crypts which might afford lodging for infection. The remarkable success of Touroff, et al.,^{81, 82} and Bourne, Keele, and Tubbs¹⁰ with ligation in the presence of subacute bacterial endarteritis may be taken as an indication that it is unlikely that patients with a ligated ductus will be likely to develop subacute bacterial endarteritis in the region of the ductus.

SUMMARY

1. Brief notes are given on 57 adults, with post-mortem examinations, who had simple, typical patency of the ductus arteriosus. A few data are presented on 10 adults with atypical patency of the ductus arteriosus.

2. Case reports are presented on four adult patients, with post-mortem examinations, who had simple patency of the ductus arteriosus.

3. In simple patency of the ductus arteriosus the cause of death was subacute bacterial endarteritis in over 40 per cent of the cases; 28 per cent died of congestive failure. Death resulted from rupture of a pulmonary aneurysm in two cases (3.3 per cent).

4. After the age of 17 years, patency of the ductus arteriosus was associated with an average reduction of life expectancy of about 25 years; this is about half the life expectancy of the general population. In the majority of cases the patient's life is fairly normal while it lasts.

5. Both right- and left-sided cardiac hypertrophy occurred in these cases, but there was no enlargement in at least 10 per cent. Pulmonary aneurysms occurred in about 15 per cent. Atheromata and calcareous plaques occurred frequently, and the aorta was involved almost as often as the pulmonary artery.

6. In these adults the ductus was usually short, and, in some cases, was represented by a fistula-like communication between the aorta and pulmonary artery. Difficult or even inoperable conditions occurred in about 17 per cent of the cases. The aortic orifice is usually larger than the pulmonary orifice.

7. A correct diagnosis of patency of the ductus can generally be made without great difficulty, but in some cases the condition cannot be recognized because of the complete absence of any murmur.

8. Among adults with simple patency of the ductus arteriosus, women predominate, representing about three-fourths of the cases. In atypical patency, however, this sex ratio seems to be reversed.

9. From analysis of the available data it is concluded that an attempt at ligation of the ductus is justifiable in spite of the absence of signs of decreasing adjustment to the defect. It must be expected that, in adults, difficult or impossible operative conditions will occur frequently.

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APPENDIX A

SIMPLE PATENCY OF THE DUCTUS IN ADULTS

These are brief notes on 57 patients, reported in the literature, who survived to the age of 17 years or more, and were examined post mortem. In each case the cause of death is given at the right-hand side of the first line.

1. CHEYERS 1845 Adult woman Tuberculosis (subacute?)
Ductus—about half as long as usual ligamentum, admitted a “common director.”
Notes—small mass of vegetations at pulmonary orifice of ductus which would act as valve preventing inflow to aorta from pulmonary artery.
2. BABINGTON 1847 34-yr.-old woman Subacute bact. endart.
Ductus—extremely short (inoperable?).
Heart—great dilatation and hypertrophy of both ventricles.
Complications—slight aortic stenosis and coarctation.
Notes—rheumatic history.
3. LUY8 1855 52-yr.-old woman Congestive failure
Ductus—admitted little finger.
Heart—right ventricle dilated and hypertrophic.
Notes—many calcified plaques in pulmonary artery.
4. ALMAGRO 1862 22-yr.-old man Congestive failure
Ductus—walnut-sized dilatation of pulmonary artery touched aorta and free communication existed between the lumens of the two vessels (inoperable).
Heart—enormously enlarged, especially right ventricle, wall of which was 2.5 cm. thick.
Notes—left lung atrophic.
5. DUROZIEZ 1862 40-yr.-old man Congestive failure
Ductus—admitted a large pea.
Heart—right auricle dilated, right ventricle greatly hypertrophied, slight atrophy of left ventricle.
Notes—no murmurs heard in life.
6. SCHNITZLER 1864 43-yr.-old woman Congestive failure with erysipelas
Ductus—diam. 5 mm. at pulmonary end, 6 mm. at aorta.
Heart—hypertrophy right ventricle.
Notes—many bony plaques in both aorta and pulmonary artery.
7. FAGGE 1873 45-yr.-old woman Congestive failure
Ductus—short, widely patent.
Heart—extreme dilatation right auricle, great enlargement tricuspid orifice, pulmonary orifice, and pulmonary artery. Both ventricles dilated and hypertrophic.
8. BUCHWALD 1878 21-yr.-old woman Subacute bact. endart.
Ductus—easily admitted thick catheter.
Heart—right side of heart almost normal, right ventricular wall thickness 3.4 mm., left side of heart much enlarged, ventricular wall 17 mm.
Complications—aneurysm (size of hen's egg) of pulmonary artery.
9. FOULIS 1884 22-yr.-old woman Subacute bact. endart.
Ductus—about 1/2 inch long, narrowest external diameter 1/4 inch, large end at aorta.

Heart—greatly enlarged, both ventricles hypertrophic, right auricle dilated. Extensive vegetations.

Complications—saccular aneurysm (size of large walnut) of pulmonary artery within pericardium.

Notes—murmurs disappeared almost entirely twenty-six days before death.

10. DARIER 1885 51-yr.-old woman Congestive failure
Ductus—round opening between aorta and pulmonary artery which were in apposition at the normal site of the ductus. (Inoperable.)
Heart—greatly enlarged, apex formed by both ventricles.
Notes—six or seven attacks of polyarticular rheumatism, but all valves normal. Fairly normal life until shortly before death.
11. W. H. WHITE 1885 53-yr.-old man Sudden death
Ductus—size of anterior tibial artery.
Heart—small, apparently entirely normal.
Complications—angina pectoris, with exacerbations and cyanosis.
Notes—died in attack of angina after one hour.
12. MURRAY 1888 36-yr.-old woman Subacute bact. endart.
Ductus—funnel-shaped, large end at aorta.
Heart—no right-sided cardiac hypertrophy.
Notes—calcification in wall of aortic side of ductus.
13. RICKARDS 1889 17-yr.-old man Subacute bact. endart.
Heart—435 gm.; left ventricle slightly hypertrophic.
Complications—mycotic aneurysm of branch of right pulmonary artery.
14. WILLIAMS 1890 40-yr.-old woman Pulmonary tuberculosis
Notes—multiple aneurysms of pulmonary artery and its branches.
15. SACHS 1892 21-yr.-old woman Subacute bact. endart.
Ductus—widely patent.
Complications—aneurysmal dilatation of main pulmonary artery, and oval aneurysm (2.5 cm. diam.) of right lower branch. Direct continuation of latter obliterated.
16. KIDD 1893 22-yr.-old woman Subacute bact. endart.
Ductus—opening to left pulmonary artery size of goose quill.
Heart—625 gm. Both sides hypertrophied and dilated, especially the left.
Complications—small saccular aneurysm of aorta close to ductus orifice. Saccular aneurysm, size of walnut, in lung, surrounded by healthy tissue. Few small tuberculous nodules, some softening to minute cavities, in lungs.
17. JOSEFSON 1897 66-yr.-old woman Sudden death
Ductus—4 mm. bore at pulmonary orifice, 6 by 10 mm. at aorta.
Heart—right ventricle hypertrophic; right auricle dilated.
Notes—this appears to be the oldest patient on record.
18. DRASCHE 1898 29-yr.-old woman Suicide
Ductus—fistula-like hole, 3 mm. bore. (Inoperable.)
Heart—small, flabby, thin-walled. No anomalies.
Notes—always well until vomited dark blood 6 months before suicide. Cause of this unexplained. Murmurs heard, but considered "accidental."
19. GIBSON 1900 31-yr.-old woman Pneumonia
Ductus—extremely short, admitted 12-14 bougie.

Heart—right ventricle dilated and hypertrophic.

Complications—delivered of seven-month-old child two weeks before death.

20. KRZYSZKOWSKI, J. 1902 17-yr.-old woman Subacute bact. endart. (?)
Ductus—diameter of a pencil.
Heart—hypertrophy of right ventricle, adhesive pericarditis at the base.
Complications—aneurysm of superior and anterior wall of pulmonary artery stem, multiple aneurysms of branches of pulmonary arteries. Marked degeneration in walls of these aneurysms.
Notes—all valves normal.
21. WEINBERGER 1903 37-yr.-old woman Congestive failure and pneumonia
Ductus—aneurysmal, thrombotic vegetations extending to wall of aorta and pulmonary artery to valve.
Heart—pulmonary valve insufficient.
Complications—repeated rheumatic and cardiac attacks for four weeks before pneumonia and failure.
22. HART 1904 23-yr.-old woman Subacute bact. endart.
Ductus—funnel-shaped, large end at aorta, patent to a middle-sized sound.
Heart—practically normal size, slight dilatation left ventricle. Embolic abscesses in myocardium.
Notes—author considered infection developed: aortic valves to ductus to pulmonary artery.
23. HART 1904 24-yr.-old woman Subacute bact. endart.
Ductus—funnel-shaped, large end at aorta, fresh embolus at pulmonary end extending into pulmonary artery.
Heart—both ventricles moderately dilated. Embolic abscesses in heart wall.
Notes—author considered infection developed: aortic valves to ductus to pulmonary artery.
24. LISSAUER 1905 24-yr.-old man Congestive failure
Ductus—15 mm. long, bore 6 mm. at pulmonary orifice, 4 mm. at aorta. At both orifices, folds of wall cut off about half of lumen.
Heart—moderate hypertrophy both ventricles, especially right.
Complications—bicuspid aortic valve. Aneurysm (size of hen's egg) of pulmonary artery. Slight hypoplasia of aorta. Marked emphysema both lungs.
25. GARIPUY 1907 28-yr.-old woman Congestive failure
Ductus—10 mm. diam., extremely short, pulmonary artery and aorta practically in apposition. (Inoperable?)
Complications—Sudden onset of failure few moments after delivery in second confinement. Died in twelve days.
26. DURNO and BROWN 1908 33-yr.-old man Ruptured pulmonary aneurysm
Ductus—widely patent, walls atheromatous.
Heart—very marked hypertrophy of right ventricle.
Complications—dissecting aneurysm of pulmonary artery ruptured into pericardium.
Notes—two weeks before death, attack of severe chest pain with vomiting; death in sleep, without warning.
27. WELLS 1908 42-yr.-old man Acute yellow atrophy
Ductus—16 mm. long, 5 mm. bore at pulmonary orifice, 8 mm. at aorta.

Heart—360 gm.; slight hypertrophy right ventricle.

Notes—cardiac symptoms unimportant in last illness.

28. HORDER 1909 42-yr.-old woman Subacute bact. endart.
Heart—510 gm.
Notes—clinical diagnosis, mitral disease.

29. MEAD 1910 26-yr.-old woman Congestive failure
Ductus—4 mm. bore at pulmonary orifice, 10 mm. at aorta.
Heart—395 gm.; both ventricles moderately hypertrophic, three ruptures of right ventricle, two ounces fluid blood in pericardial sac.
Complications—slight aortic and mitral stenosis, rheumatic history. Scoliosis. Complete paralysis left vocal cord.

30. SOMMERS 1910 45-yr.-old woman Subacute bact. endart.
Ductus—cone shaped, size of hazelnut at aortic orifice.
Heart—hypertrophy and dilatation of right ventricle.
Notes—ulcerative endocarditis of aortic valves and vegetations covering wall of ductus and of pulmonary artery all way back to pulmonary valves.

31. MOTZFELDT 1913 35-yr.-old man Sudden death; cause uncertain
Ductus—small caliber.
Heart—both ventricles slightly hypertrophic.
Notes—no mention of any murmur in previous medical history.

32. MOTZFELDT 1913 55-yr.-old woman Congestive failure
Heart—700 gm. Hypertrophy and dilatation of right ventricle.

33. MOTZFELDT 1913 32-yr.-old man Tuberculous pneumonia
Ductus—8 mm. diameter, extremely short, practically fistula between aorta and pulmonary artery. (Inoperable.)
Heart—590 gm. Both ventricles hypertrophic, especially right.
Notes—cardiac symptoms unimportant in last illness.

34. HAMILTON and ABBOTT 1914 19-yr.-old woman Subacute bact. endart.
Ductus—7.5 mm. long, "admitting a penholder."
Heart—slight hypertrophy and marked dilatation right ventricle. All endocardial structures normal.
Complications—mycotic aneurysm of pulmonary artery. Slight coarctation of aorta (6 cm. circumference at origin, 5 cm. at left subclavian, 4 cm. in descending portion).

35. STODDARD 1915 17-yr.-old woman Subacute bact. endart.
Ductus—8 mm. long; bore, 5 mm.
Heart—very slightly enlarged.

36. CAYLOR 1918 40-50-yr.-old woman Ruptured aortic aneurysm
Ductus—diameter 3.5 mm. at pulmonary artery; 6 mm. at aorta.
Heart—485 gm.; wall thickness, left ventricle, 11 to 24 mm., right ventricle, 4 to 8 mm.
Complications—ruptured aortic aneurysm, easily contained a whole fist.
Notes—diagnosis of patent ductus made twenty-one years before death, while still in apparently fair health; the thrill and machinery murmur disappeared, and were replaced only by poorly defined systolic murmur in pulmonary area.

37. BAÜMLER 1919 36-yr.-old woman Congestive failure
Ductus—wide, funnel-shaped, large end at aorta, no actual vessel (less than 0.5 mm. long).
Heart—much enlarged right ventricle; left normal.
Complications—miliary and nodal tuberculosis of lungs.
Notes—this patient observed eighteen years (when strong and well) until death.
38. HUBENY 1920 57-yr.-old woman Ruptured aortic aneurysm
Heart—marked left-sided cardiac hypertrophy and dilatation.
Complications—syphilitic aortic aneurysm observed, but not recognized in roentgenogram before rupture.
Notes—diagnosis of patent ductus made twenty years before death. Shadow of aortic aneurysm seen shortly before death, but ascribed to patent ductus.
39. WELLS 1922 50-yr.-old man Cerebrovascular accident
Ductus—coneshaped, 10 mm. at aortic end, 5 mm. near pulmonary orifice, latter closed to 1 or 2 mm. bore by fold of soft membrane protruding into pulmonary artery.
Heart—400 gm.; both ventricles dilated. No anomalies.
Notes—soft mitral murmur, not transmitted, only cardiac sign observed in few hours before death.
40. BOLDERO and 1924 29-yr.-old man Subacute bact. endart.
BEDFORD
Ductus—15 mm. long.
Heart—greatly enlarged; both ventricles hypertrophic.
Complications—history of rheumatic fever.
Notes—2 small calcified areas in aortic wall near ductus. Blood pressure 200/90 before onset of subacute bact. endarteritis.
41. MOENCH 1924 29-yr.-old woman Ruptured pulmonary
aneurysm
Ductus—admitted index finger.
Heart—mitral valve thickened; pulmonary valve bicuspid.
Complications—aneurysmal dilatation (3 inches in diameter) of pulmonary artery, ruptured into pericardium. Lungs congested.
Notes—small plaques of atheromata in aorta. No previous symptoms except slight exertional dyspnea.
42. TERPLAN 1924 35-yr.-old woman Subacute bact. endart.
Ductus—bore 2 mm.
Heart—hypertrophy and dilatation of left ventricle.
43. HAMMERSCHLAG 1925 51-yr.-old woman Subacute bact. endart.
Ductus—true mycotic aneurysm of ductus.
Heart—both ventricles hypertrophic.
Notes—histologic studies proved true aneurysm of ductus.
44. ROTH 1927 23-yr.-old woman Subacute bact. endart.
Ductus—5 mm. long, ulcerative endarteritis at pulmonary orifice.
Heart—moderately enlarged, fatty degenerative changes in myocardium.
45. von SCHULEZ 1928 25-yr.-old woman Congestive failure
Ductus—admitted pencil.
Heart—very marked hypertrophy and dilatation of right ventricle.
Complications—five months pregnant, surgical abortion planned after return to compensation, but she died before this was achieved.

46. P. D. WHITE 1928 65-yr.-old woman Cerebrovascular accident
Ductus—22.5 mm. long, 4 mm. bore at pulmonary artery, 10 mm. at aorta.
Heart—430 gm.; both ventricles hypertrophic. Severe sclerosis of coronaries, also aortic and mitral valves, aorta, and papillary muscles of left ventricle.
Notes—pulmonary artery smooth and normal. First noted heart trouble at age of 40 years.

47. KASAKOFF 1929 26-yr.-old woman Subacute bact. endart.
Ductus—5 mm. long; diameter, 5 mm.
Heart—both ventricles hypertrophic; wall thickness: left, 23 mm., right, 10 mm.

48. PALLASSE and 1930 47-yr.-old man Congestive failure
 CHANALEILLES
Ductus—practically fistula between aorta and pulmonary artery, 12 mm. diam.
 Organized clot almost obliterated free lumen. (Inoperable.)
Heart—700 Gm. Right ventricle more hypertrophic than left.
Complications—rheumatism at age 7.

49. WEISS 1931 33-yr.-old woman Subacute bact. endart.
Heart—350 Gm.
Notes—patient had five children, two miscarriages. Wassermann 4+. Dislike calcified plaque at aortic orifice of ductus.

50. FISCHER and SCHUR 1932 30-yr.-old woman Subacute bact. endart.
Ductus—easily patent to thick sound.
Heart—left ventricle hypertrophic.
Notes—questionable history of rheumatic fever few years earlier.

51. PERRY 1933 35-yr.-old woman Subacute bact. endart.
Notes—first diagnosed patent ductus and pulmonary tuberculosis.

52. d'AUNOY and 1934 32-yr.-old man Subacute bact. endart.
 von HAAM
Ductus—15 mm. long.
Complications—aneurysm of pulmonary artery. Syphilis.

53. BRODY and 1935 66-yr.-old woman Congestive failure
 RANDELL
Ductus—14 mm. long, diameter 4 mm. at pulmonary artery, 9 mm. at aorta.
Heart—both ventricles enlarged.
Notes—congenital polycystic kidney, ureter absent. No symptoms except palpitation until age of 62 years. Died at age of 65 years, 11½ months.

54. HINES and WOOD 1935 18-yr.-old woman Subacute bact. endart.
Ductus—bore about 2-3 mm.
Heart—great dilatation of both sides; not much hypertrophy.
Notes—pulmonary valve leaflets completely destroyed, pulmonary artery and ductus almost filled with vegetations, other valves normal, two small polypoid vegetations on aortic side of ductus.

55. MALLORY 1938 21-yr.-old woman Subacute bact. endart.
Ductus—aorta and pulmonary artery in apposition and communicating by a small round hole at the usual site of the ductus arteriosus. (Inoperable.)

56. GRENET, LEVENT 1939 17-yr.-old woman Subacute bact. endart.
and JOLY
Ductus—5 to 10 mm. long; small caliber.
Heart—both sides dilated and hypertrophic.
Notes—no dilatation of pulmonary artery.
57. BETTINGER 1941 40-yr.-old woman Congestive failure
Ductus—8 mm. long; 7.5 mm. in diameter. Wall rigid with calcifications.
Heart—extreme hypertrophy right ventricle (wall thickness up to 20 mm.).
Complications—died of failure seven days after pelvic operation from which she failed to rally.

APPENDIX B

ATYPICAL PATENCY OF THE DUCTUS IN ADULTS

1. CHEVERS 1845 Young man Pneumonia
Ductus—about 4 mm. communication between aorta and pulmonary artery, which were in apposition at usual site of ductus. (Inoperable.)
Complications—considerable constriction of aorta above site of communication with pulmonary artery.
2. HEBB 1893 40-yr.-old man Pulmonary tuberculosis
Ductus—aneurysmal (size of walnut) filled with firm laminated clot.
Heart—verrucose endocarditis of aortic valve.
Complications—complete obliteration of left branch of pulmonary artery and marked stenosis of left branch at its origin.
Notes—no cardiac anomaly suspected during life.
3. HOCHHAUS 1893 24-yr.-old man Subacute bact. endart.
Ductus—diameter about 6 mm. in middle, 7 mm. at pulmonary end, 14 mm. at aortic end.
Heart—greatly dilated and hypertrophic.
Complications—marked stenosis of aortic arch just before orifice of the ductus.
Notes—there was a prominent diastolic murmur as well as the usual prolonged systolic murmur.
4. WAGENER 1903 38-yr.-old woman Pneumonia
Ductus—16 mm. long, 7 mm. bore except at pulmonary orifice, which was closed by membrane except for pinhole communication.
Heart—normal.
Notes—no dilatation of pulmonary artery.
5. WAGENER 1903 42-yr.-old man Postoperative peritonitis
Ductus—funnel-shaped pouch in aorta projected into pulmonary artery; this pouch was pierced by two very small holes. Considered patent ductus by pathologist.
Heart—chronic endocarditis of aortic valves, slight stenosis of aortic and pulmonary valves.
Notes—no murmurs in life.
6. MOENCKEBERG 1924 35-yr.-old man Congestive failure?
Ductus—aneurysmal (half size of apple), filled with clot, not patent throughout. No trace of ligamentum arteriosum.
Heart—marked eccentric (right-sided) hypertrophy.
Notes—marked paralysis of left vocal cord. Clinical diagnosis was "war nephritis."

7. HALL 1926 32-yr.-old man Congestive failure
Ductus—bore, 3 mm.
Heart—greatly enlarged (860 gm.), chiefly left ventricle. Aortic ring dilated and insufficient.
Complications—healed dissecting aneurysm of aorta near valve.
8. PAUL 1930 36-yr.-old man Erysipelas
Ductus—patent to a thick sound.
Heart—770 gm., both sides equally enlarged.
Complications—isthmus stenosis of aorta sharply confined to point opposite orifice of ductus.
Notes—rheumatic fever at 28 years.
9. ULRICH 1932 23-yr.-old man Sudden failure
Ductus—formed principal source of blood supply to the descending aorta.
Heart—870 Gm., both sides greatly enlarged, but right more so than left; right ventricle wall thickness 10 to 20 mm., left 15 to 30 mm.
Complications—aortic arch greatly constricted between left subclavian and insertion of ductus, hypoplastic descending aorta. Cirrhosis of the liver (2,725 gm.). Bundle branch block.
Notes—worked as farm laborer without trouble until development of ascites.
10. GRAHAM 1940 31-yr.-old man Hem. at operation
Ductus—aneurysmal, filled with partly organized clot, pulmonary end obliterated.
Heart—moderate hypertrophy left ventricle, patent foramen ovale (probably functionally closed), right aortic arch.
Notes—preoperative diagnosis was mediastinal tumor.

(See discussion on page 205.)

THE RESULTS OF SURGICAL TREATMENT OF PATENCY OF THE DUCTUS ARTERIOSUS COMPLICATED BY SUBACUTE BACTERIAL ENDARTERITIS

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INTRODUCTION

THE first surgical cure of subacute bacterial endarteritis involving a patent ductus arteriosus was reported by Touroff and Vesell¹ in 1940. Although additional operative cures have been recorded since then by the author and others,²⁻⁸ statistics concerning the general results of surgical treatment of infected patent ductus arteriosus are not as yet available. Accordingly, it may be of interest to report a series of eleven patients who have been operated upon during the past two and one-half years.

When the first of these patients was subjected to operation (in January, 1940), the only reference in the literature to the surgical treatment of patency of the ductus arteriosus complicated by subacute bacterial endarteritis was a report of a single unsuccessful attempt at ligation of the duct by Graybiel, Strieder, and Boyer⁹ (1938).† Thus, in the absence of any knowledge of how the superimposed infection might respond to surgical therapy, operation was undertaken purely empirically. Much to our gratification, the patient not only survived, but also recovered promptly. Subsequently, ten additional patients were operated upon; and it is the purpose of the present communication to set forth the results which were obtained and to discuss some of the factors which appear to influence the outcome of operation. At the outset, it may be stated that although not all of our patients were cured, the value of surgical therapy in properly selected cases was firmly established.

FACTORS INFLUENCING THE OUTCOME OF OPERATION

In a previous communication,⁶ it was indicated that proper evaluation of surgical therapy necessitates an appreciation of the fact that the pathologic process in the ductus and adjoining structures may vary considerably in severity and extent, and that the outcome of operation is influenced largely by such pathologic changes. Abbott¹¹ has pointed out that vegetations usually develop initially at the pulmonic end of the ductus and in the adjacent portions of the pulmonary artery, and that, at a later stage of infection, they may involve the cardiac valves or ex-

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†The first successful ligation of a patent ductus arteriosus (uncomplicated by infection) was reported by Gross and Hubbard¹⁰ in 1939.

tend into the aorta. It has already been demonstrated that, if operation is performed while the vegetations remain confined to the pulmonic end of the ductus and the pulmonary artery, a cure may be anticipated fairly regularly.⁶ On the other hand, if vegetations have already spread to the cardiac valves or into the aorta, operation fails to prevent the growth of these new vegetative lesions,¹² and the latter continue to act as foci from which infective material is released into the peripheral circulation.

The severity and extent of pathologic changes involving the ductus and adjacent tissues, in addition to influencing the late results of surgical treatment, also determine in large measure the actual hazards of the operation. In previous communications,^{6, 12} it was pointed out that the greatest of these dangers is accidental hemorrhage resulting from injury of the ductus as the latter is being separated from the adjacent tissues—chiefly the pulmonary artery and left main bronchus—preliminary to ligation. In the earliest stages of infection, the inflammatory process involves only the intima of the ductus. Subsequently, however, it may involve more and more of the thickness of the wall of the ductus. At a still later stage, the inflammation may extend to the adventitia and surrounding tissues; the ductus then usually becomes adherent, in varying degree, to the adjacent structures. As the wall of the ductus becomes extensively diseased, it tends to become indurated and friable; and the local inflammatory process sometimes may be so destructive that mycotic aneurysms¹¹ are formed. Friability of the ductus (or aneurysm) and adherence to the surrounding structures greatly increase the likelihood of inadvertent tearing of the ductus as the latter is being manipulated. The hemorrhage which results from such an accident is often difficult to control and is not infrequently fatal. From all of the foregoing it is apparent that the earlier the operation is performed, the greater is the likelihood of cure and the less are the chances of operative hemorrhage. In this connection it is germane to discuss briefly the danger of prolonged chemotherapy.

It is now rather generally agreed that if chemotherapy is to prove curative in cases of subacute bacterial endarteritis, evidence of infection will subside and blood cultures will become sterile fairly promptly. Accordingly, if this does not occur within two or three weeks, the likelihood of recovery becomes increasingly remote. In spite of this oft-repeated dictum, there is a general tendency to continue the administration of sulfonamide drugs after the latter have proved ineffectual. Such a policy may be excusable in cases of subacute bacterial endarteritis of the usual type, because other forms of treatment are of little or no value. In cases of subacute bacterial endarteritis involving a patent ductus, however, prolonged chemotherapy may jeopardize the patient's chances of recovery by delaying operation unduly. Judging from the general lack

of effectiveness of preoperative chemotherapy in the cases of the present series, and in other cases in which no operation was done, I am of the opinion that the interests of the patient are best served by proceeding with operation as soon as the diagnosis of superimposed infection has been established. Although this viewpoint may appear radical, it is based upon the following observations: (1) the low incidence of recovery with chemotherapy alone, (2) the variable outcome in cases in which chemotherapy is employed for long periods prior to operation, and (3) the high incidence of recovery after operation, when the latter is performed *before* vegetations have spread to the cardiac valves or into the aorta. The effectiveness of surgical therapy in the last group is demonstrated particularly by the fact that recovery ensues without chemotherapy after operation (Table II). To summarize, it may be stated that the role of chemotherapy should be that of an adjuvant, and not a substitute for operation.

PREOPERATIVE DATA

Of the eleven patients in this series, eight were women. The patients ranged in age from 9 to 63 years.* Five were in the third decade, two in the fourth decade, and one each in the first, second, sixth, and seventh decades of life. It appeared significant that, in nine of the eleven patients, infection occurred during or after the third decade.†

In ten cases the duration of infection, from the time of onset of clinical manifestations to the time of operation, varied between thirty-one (+) days and five months. In the remaining case (Case 11), which was altogether unique, infection had been present for two years prior to operation.‡ Despite the fact that the majority of the blood cultures had been positive since the onset of the illness, the patient remained in surprisingly good physical condition and exhibited few of the stigmata of subacute bacterial endarteritis (endocarditis) of long duration.

Five patients had spontaneous pulmonary embolism prior to operation (Cases 3, 6, 7, 10, and 11). One of these also developed splenic infarction (Case 10). Another patient had renal infarction (Case 2). The preoperative peripheral embolism in the last two cases (Cases 2 and 10) was

*The wide variation in age (9 to 63 years) re-emphasizes a point made in previous communications,^{6, 12} namely, that subacute bacterial endarteritis may occur at any age, and that it constitutes a perpetual threat to the patient with a patent ductus arteriosus. In this connection, it is to be stressed that the patient with a patent ductus arteriosus should be kept under observation throughout life, and a blood culture taken promptly if fever of obscure origin appears.

†This is assumed to be caused by two factors. The first is that foci of *Streptococcus viridans* infection (teeth, tonsils, etc.), which presumably constitute the original portal of entry, are much more common in adults than in children. The second is that atheromatous plaques, which constitute the primary sites of development of vegetations, usually do not make their initial appearance until adult life.

‡Two patients with the chronic form of subacute *Streptococcus viridans* infection were also operated upon. Both presented typical stigmata, including profound anemia, café-au-lait color, repeated crops of petechiae, great splenic enlargement, amyloidosis, renal involvement, and clubbing of the fingers. In one case, the diagnosis of infection of a patent ductus arteriosus was confirmed at operation. In the other, the ductus was not open, and it was assumed that the congenital cardiac lesion was, in all probability, a septal defect. These two patients were placed in a special experimental group in advance of operation because there seemed little likelihood that they would recover completely even if operation were carried out successfully. They will not be discussed here, but will be the subject of a separate report.

attributed to vegetative lesions upon the mitral and aortic valves; and the persistence of the latter lesions after operation accounted for the failure of these patients to recover from their infection.

Evidence of cardiac failure was present in three cases (Cases 3, 6, and 7) at the time of operation; and it appears significant that this occurred in the two oldest patients of the series (aged 51 and 63 years, respectively). Both of the latter were free of manifestations of circulatory failure during childhood and early adult life. Thus, although compensation was adequate in the beginning, cardiac failure supervened as the myocardium began to undergo late degenerative changes. Incidentally, the fact that infection and cardiac failure first occurred so late in life constitutes a powerful argument in favor of prophylactic operation during childhood.

Ten patients received chemotherapy prior to operation (either before or after admission to the hospital) without significant effect; the remaining patient (Case 1) did not receive chemotherapy. At the time of operation, all patients presented clinical and laboratory evidence of active infection and all had positive blood cultures (*Streptococcus viridans*).

In all cases, the characteristic "machinery" murmur of patent ductus arteriosus was present. Several of the patients had additional soft systolic murmurs (at the apex or base) which were considered to be of little significance. In two cases (Cases 2 and 10), the presence of characteristic murmurs led to the additional preoperative diagnosis of secondary, vegetative valvular involvement.* It was assumed in advance that operation would fail in these two cases; but, in order to either establish or disprove this point, it was decided to proceed.

TABLE I
RESULTS OF SURGICAL TREATMENT IN ELEVEN CASES

A. Operative Survivals	9
Cured	6
(See Table II.)	
Not Cured	3
(a) Two patients with preoperative spread of vegetations to the cardiac valves	
(b) One patient with preoperative extension of vegetations into the aorta	
(See Table III.)	
B. Operative Deaths	2
Both caused by hemorrhage from injury to a friable, adherent ductus (prior to modification of operative technique).	
(See Table III.)	

*The diagnosis in these two cases was further substantiated by the occurrence of peripheral embolism prior to operation.

THE RESULTS OF OPERATION

The operation consisted of ligation of the ductus in nine cases and division of the ductus in two (Cases 1 and 7). Among the eleven cases, there were nine operative survivals and two operative deaths (from hemorrhage).

The two fatalities occurred early in the series¹² (Cases 3 and 4), before the present modification of operative technique was developed.¹³ Post-mortem examination in Case 3 disclosed that the vegetations were confined exclusively to the ductus and pulmonary artery. At autopsy in Case 4, vegetations were found at the above sites; and a few pin-point verrucae, the significance of which was uncertain, were noted upon the pulmonic valve (Table I).

Of the nine surviving patients, six recovered from their infection.* In none of the latter cases was recovery attributable to chemotherapy.† Furthermore, the rapidity with which the blood cultures became sterile was startling (see Table II). (This aspect of the first five cases has already been presented briefly.^{1, 6, 7, 8} A detailed report of the bacteriologic investigations in all eleven cases will be published in the near future.)

Recovery in four of the six cases was entirely uneventful. In the remaining two cases, minor complications occurred. These consisted of two attacks of mild, left-sided pulmonary infarction in Case 1, and of a superficial wound infection in Case 5. The longest postoperative stay in the hospital was thirty-four days (Case 5); the shortest was thirteen days (Cases 6 and 8).

All six patients have had repeatedly negative blood cultures, have been free of clinical and laboratory evidences of infection, and are carrying on normal activities at the present time. The two patients who had circulatory failure prior to operation (Cases 6 and 7) are entirely free of this complication. The follow-up period varies from three to twenty-nine months (see Table II).‡

Three of the nine surviving patients (Cases 2, 9, and 10) continued to have positive blood cultures after operation. Prior to operation, two of them (Cases 2 and 10) had peripheral embolism, and presented apical and basal murmurs indicative of valvular involvement, in addition to

*The rationale of ligation of the ductus when a patent ductus arteriosus is complicated by subacute bacterial endarteritis has been discussed elsewhere.¹⁴

†One of these patients (Case 1) received 9 grams of sulfapyridine on the fifth postoperative day, after all postoperative blood cultures prior to that time had remained sterile.¹ Another patient (Case 5) received 10 grams of sulfapyridine on the twelfth postoperative day, after all postoperative blood cultures prior to that time also had been negative.⁶ (In Case 1, the drug was employed because of an acute postoperative febrile reaction. In Case 5, it was used because of continuing fever of obscure origin.) In view of the already sterile postoperative blood cultures, before chemotherapy was begun, it appears warranted to maintain that the sulfonamides played no role in the recovery of either of these patients. In the remaining four cases, chemotherapy was not employed after operation. To the best of my knowledge, these are the only cases so far reported in which chemotherapy was withheld after operation in an attempt to test the effectiveness of operative therapy alone. The results demonstrate conclusively that operative occlusion of the ductus, per se, is curative.

‡Cardiovascular studies in these cases will be reported in detail in a separate communication.

TABLE II
SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS
6 CURED PATIENTS

CASE, NAME AGE, SEX	DURATION OF INFECTION	PRE-OPERATIVE CHEMOTHERAPY	BLOOD CULTURES		OPERATION DATE AND TYPE	POST-OPERATIVE BLOOD CULTURES		POST-OPERATIVE CHEMOTHERAPY	RESULT
			NO. OF COLONIES	LAST PRE- OPERATIVE CULTURE		INITIAL CULTURE(S)	SUBSEQUENT CULTURES		
1 S. S., 29 Female	3 Months	None	50-400	1/24/40 Heavily positive	1/27/40 Division of ductus	1/29/40 Sterile	6 All sterile	Sulfapyridine 9 gm. on 5th day (blood cultures already sterile)	Well 28½ Months
5 P. S., 29 Female	3½ Days	Poorly tolerated (Sulfapyridine)	0-177	6/14/41 9:00 A.M. 80 col./c.c.	6/14/41 3:15 P.M. Ligation of ductus	6/14/41 6:15 P.M. Sterile	11 All sterile	Sulfapyridine 10 gm. on 12th day (blood cultures already sterile)	Well 12 Months
6 G. O., 51 Female	8 Weeks	Poorly tolerated (Sulfapyridine sulfathiazole)	40-52	8/25/41 52 col./c.c.	9/4/41 3:30 P.M. Ligation of ductus	9/4/41 4:10 P.M. Sterile	4 All sterile	None	Well 9 Months
7 J. Z., 18 Female	4 Months	Well tolerated (Sulfathiazole)	70-120	9/27/41 2:00 P.M. 120 col./c.c.	9/27/41 3:49 P.M. Division of ductus	9/27/41 4:00 P.M. 1 col./c.c. 4:30 P.M. 1 col./c.c.	7 All sterile	None	Well 8½ Months

8 H. N., 9 Male	5 Weeks	Well tolerated (Sulfadiazene)	2-88	1/9/42 3:02 P.M. Heavy growth in flask	1/9/42 3:04 P.M. Ligation of ductus	1/9/42 3:14 P.M. Sterile 3:34 P.M. Sterile 4:10 P.M. Sterile 5:10 P.M. 1 col./4 c.c. 10:10 P.M. 1 col./4 c.c.	1/10, 11, 13, 15 Sterile 1/17 1 col./20 c.c. Thereafter 7 All sterile	None	Well 5 Months
11 H. S., 31 Male	24 Months	Well tolerated (Sulfadiazene, sulfathiazole, sulfapyridine & sulfanilamide)	0-143	3/24/42 2:58 P.M. 54 col./c.c.	3/24/42 3:10 P.M. Ligation of ductus	3/24/42 3:16 P.M. 7 col./c.c. 3:26 P.M. Plates sterile Flasks positive 3:43, 4:10, 5:10, 6:10, 8:10 & 11:10 P.M. All sterile	3/25, 26, 28, 29, 31 & 4/3 Sterile 4/7 Flask positive Thereafter 4 All sterile	None	Well 11 Weeks

TABLE III
SUBACUTE STREPTOCOCCUS VIRIDANS ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS
5 OPERATIVE FAILURES

CASE NAME SEX AGE	DURATION OF INFECTION	PREOPERATIVE CHEMOTHERAPY	PREOPERATIVE BLOOD CULTURES	OPERATION DATE AND TYPE	POSTOPERATIVE BLOOD CULTURES	CAUSE OF FAILURE	RESULT FOLLOW-UP
2 G.F. Female 29	5 Weeks	Well tolerated (sulfapyridine)	15-50 col./c.c.	2/8/40 Ligation of ductus	All positive, despite chemotherapy	Vegetations upon aortic valve	Died of original infection 8 mo. after operation
3 A.S. Female 63	5 Months	Well tolerated (sulfanilamide, sulfapyridine and heparin)	6-30 col./c.c.	3/16/40 Attempted ligation of ductus	→	Operative hemorrhage (from a friable, adherent ductus)	Death. Vegetations confined to ductus and pulmonary artery.
4 J.S. Female 24	3 Months	Well tolerated (sulfanilamide and sulfapyridine)	32-72 col./c.c.	4/8/40 Attempted ligation of ductus	→	Operative hemorrhage (from a friable, adherent ductus)	Death. Vegetations in ductus and pulmonary artery and upon pulmonary valve (pinpoint verrucae)
9 C.B. Female 20	9 Weeks	Well tolerated (sulfadiazine)	25-30 col./c.c.	2/19/42 Ligation of ductus	All positive, despite chemotherapy	Vegetations within aorta (or aortic end of ductus)	Unimproved 16 weeks after operation
10 I.A. Male 33	4½ Months	Well tolerated (sulfapyridine and sulfathiazole)	15-27 col./c.c.	3/3/42 Ligation of ductus	All positive, despite chemotherapy	Vegetations upon mitral and aortic valves	Unimproved 14 weeks after operation

evidences of a patent ductus. The last patient (Case 9) presented no such preoperative phenomena, and it was, therefore, concluded that the continuing postoperative bacteremia was not caused by valvular vegetations, but by vegetations within the ductus on the aortic side of the ligature. This conclusion appeared to be substantiated by the occurrence, for the first time, of splenic infarction nine days after operation.*

The subsequent fate of these three patients is indicated in Table III.

DISCUSSION

Prior to operation, seven of the nine surviving patients presented no evidence of vegetative valvular lesions or peripheral embolism. (Red-centered petechiae are not classed as embolic lesions.) Of these seven patients, six were cured, and one continued to have active bacteremia, due to vegetations at the aortic end of the ductus. The remaining two of the nine patients presented auscultatory evidence of valvular lesions and had peripheral embolism prior to operation. These patients continued to have bacteremia after operation.

The foregoing analysis re-emphasizes the fact that when vegetations remain confined to the pulmonic end of the ductus and pulmonary artery, peripheral embolism is not likely to occur, and operation, if carried out successfully, is likely to be followed by recovery from the infection. On the other hand, when vegetations have spread to the cardiac valves, mitral or aortic, peripheral embolism occurs and characteristic murmurs are likely to be present prior to operation. In cases of the latter type, operation does not benefit the patient.

When vegetations are present at the aortic end of the ductus, they may produce no unusual murmurs and may not result in peripheral embolism prior to operation. In such cases, therefore, it may be impossible to make the diagnosis. In this connection, it should be pointed out that when vegetations actually extend into the aorta they may not produce new murmurs, but they are often responsible for peripheral embolism prior to, and after, operation. In such cases, also, operation is not advisable.

It appears that spread of vegetations to the pulmonic valve is difficult to recognize prior to operation. Thus, in Case 4, in which several verrucae were present at that site, the patient presented no unusual manifestations. Although valvular murmurs may have been present, they might easily have been obscured by the loud, roaring machinery murmur. Likewise, if emboli were being thrown off, they were probably trapped in the lung, so that peripheral embolic manifestations were pre-

*In view of the fact that the current through the ductus flows from the aorta toward the pulmonary artery, it is assumed that emboli derived from vegetations close to the aortic end of the ductus normally are swept into the pulmonary circuit.¹³ After the ductus is ligated, however, vegetations which remain on the proximal side of the ligature release their emboli into the aortic blood stream. This appears to explain the initial occurrence of peripheral embolism after operation in Case 9. If peripheral embolism had been the result of vegetations within the aorta, one would expect it to have occurred prior to operation as well as afterward.

vented. Whether or not a patient with right-sided, vegetative valvular lesions can be cured by operation still remains uncertain.

Although the secondary development of vegetations upon the cardiac valves is most likely to occur when the infection is prolonged, it appears that the duration of infection is not the only factor. For example, in Case 2, vegetations developed upon the aortic valve after only five weeks of illness; whereas, in Case 11, spread did not occur despite the fact that the infection had been present for two years. It is apparently significant that the clinical course in Case 2 was of the severely septic type, whereas in Case 11 it was unusually mild. Thus, severity of infection appears to be an additional factor in determining the rapidity of spread to the valves. This point was substantiated by a review of the remaining cases of the series. Finally, the configuration of the ductus seems to play a role in determining the outcome of the operation.

Abbott¹¹ has demonstrated that the ductus may vary in shape from a well-defined tubular structure to an arteriovenous fistula in which the ductus consists merely of an opening between the aorta and pulmonary artery. This has been demonstrated at operation, also. Whereas vegetations develop initially at the pulmonic end of a ductus of average length, those within a short ductus are likely to involve practically its entire length. Thus, when a short ductus is ligated, it may be impossible to place the ligature beyond the vegetations at the aortic end, and so exclude the vegetations from contact with the aortic blood current. As a result, any vegetations which remain on the proximal side of the ligature continue to launch infective material directly into the aorta, and the bacteremia persists. This was apparently the cause of failure in Case 9, in which the ductus was found at operation to be relatively short in proportion to its diameter and joined to the aorta by a wide funnel-like mouth.

INDICATIONS AND CONTRAINDICATIONS TO OPERATION

It has already been demonstrated that the mere presence of additional cardiac murmurs is not a reliable indication of the existence or location of new vegetative lesions. Thus, chief reliance must be placed upon the occurrence of peripheral embolism in deciding whether or not operation should be performed. If peripheral embolic lesions are unquestionably present, operation appears to be contraindicated. On the other hand, if such embolic lesions have not occurred, the patient is entitled to operation even if murmurs, suggesting the presence of valvular lesions, exist. Although operation in doubtful cases may not always result in recovery from infection, it offers the patient his only remaining chance and, therefore, should be undertaken without hesitation.

Aside from incontrovertible evidence of spread of vegetations, as indicated by the occurrence of peripheral embolic lesions, the only absolute contraindication to operation is clear-cut evidence of the presence of

associated, major congenital cardiovascular anomalies, for which the patent ductus acts as a compensating lesion. Under the latter circumstances, the current through the ductus flows from the pulmonary artery into the aorta, and the resultant inadequate oxygenation of the blood produces cyanosis and clubbing of the fingers. Ligation of the ductus in such cases usually leads rapidly to circulatory embarrassment and death.

In certain cases, patency of the ductus arteriosus may be associated with some minor congenital cardiovascular anomaly. If the presence of an associated cardiovascular anomaly is suspected or has been demonstrated by angiocardiology, but the patient is not cyanotic, it may be concluded that the lesion in question is of minor significance and that it is safe to proceed with operation. In this connection, however, it must be remembered that vegetations are prone to develop at sites of associated cardiac anomalies, regardless of whether the latter are major or minor. If vegetations already are present at such sites, the course of events is likely to be as little influenced by ligation of the duct as it is in cases in which vegetations have spread to the cardiac valves or aorta. If vegetations have not already become engrafted upon the associated minor anomaly, however, operation may prove curative.

There still seems to be some hesitation, on the part of certain internists, to advise surgical treatment of patency of the ductus arteriosus when the ductus is the seat of subacute bacterial endarteritis. This may be due primarily to fear that the surgical procedure is of such magnitude that it may not be withstood by patients who are either very acutely ill or are debilitated by prolonged infection. The cases described herein demonstrate that such an attitude is no longer justifiable; for, with the exception of two patients who died of hemorrhage early in the series, the remainder withstood the operation without difficulty. In Case 6, for example, the patient, aged 51 years, suffered not only from infection, but also from cardiac failure and recent pulmonary infarction. Case 7 demonstrates, in a convincing manner, that poor general physical condition is not a contraindication to operation. On the contrary, rapid worsening of the patient's condition and the prospect of early fatality constitute powerful arguments in favor of prompt surgical intervention. Because of certain unusual features, Case 7 appears worthy of brief presentation.

REPORT OF CASE

History.—J. Z., a native-born white girl, aged 19 years, was admitted to the medical service of Beth Israel Hospital September 24, 1941. She was known to have had heart trouble since the age of one and one-half years. Since earliest childhood, she had been thin and underdeveloped, and she suffered from dyspnea and fatigue on mild exertion. The remainder of the past history was irrelevant.

About four months prior to admission she developed irregular fever and lassitude and began to lose weight. At that time, the diagnosis of patency of the ductus arteriosus was made, but no specific treatment was recommended (Fig. 1). After two months of continuing symptoms, she had an attack of severe pain in the left side of the chest. Two weeks later she was admitted to another hospital, suffering from

sweats, irregular fever (ranging from 101° to 105° F.), chills, pain in the left side of the chest, and dyspnea. At that time, four blood cultures were positive for *Streptococcus viridans*, and roentgenologic examination of the chest revealed evidence of patency of the ductus arteriosus and left-sided pulmonary infarction. The electrocardiogram at first was negative, but one month later revealed right axis deviation.

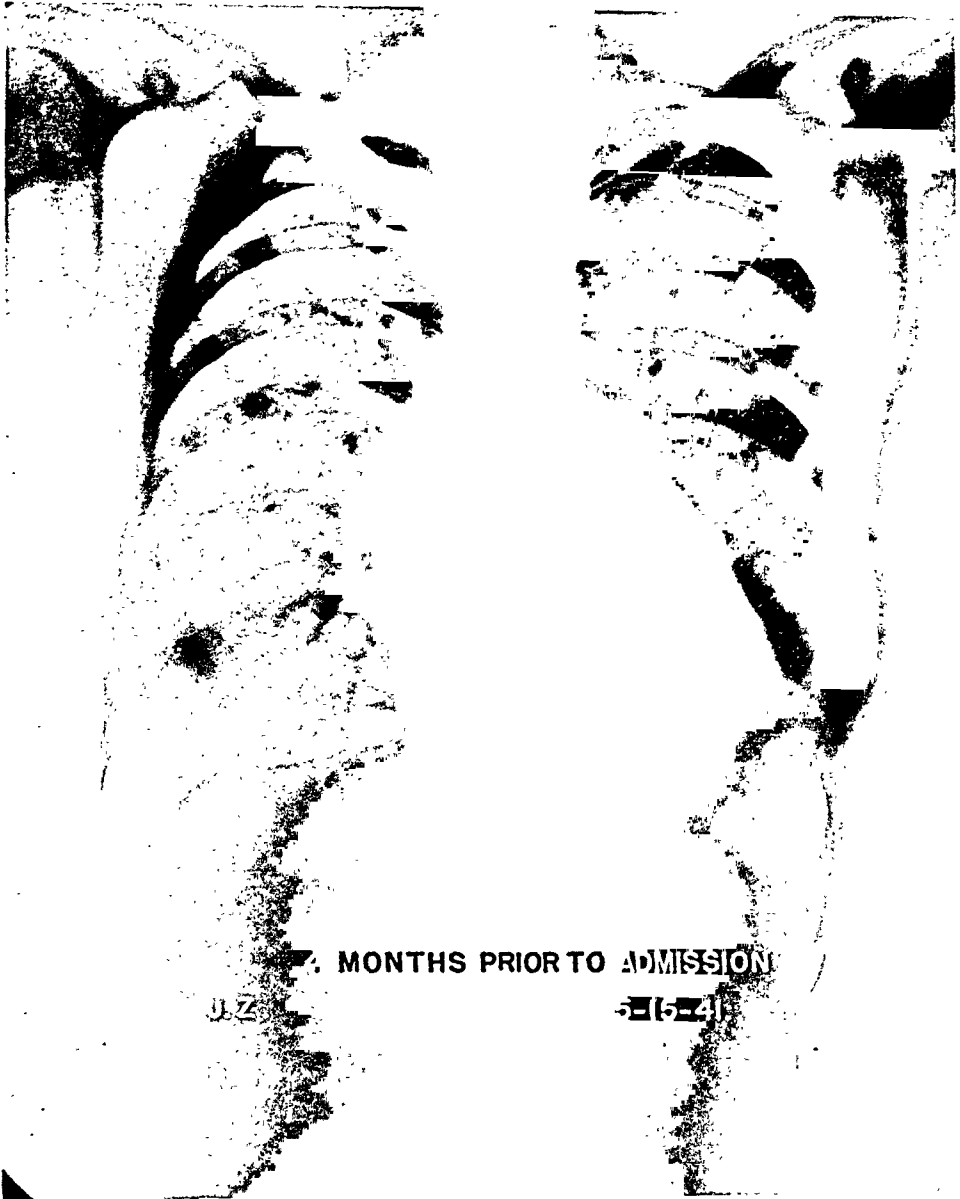


Fig. 1.—Roentgenogram of chest four months prior to admission to the hospital. Note enlargement of the heart, prominence of the region of the pulmonic conus, and pulmonary vascular congestion.

The blood pressure on admission was 130/70, but later the diastolic pressure could not be obtained. Large doses of sulfathiazole were administered throughout the hospital stay, but no significant effect was produced. At the end of five weeks she was discharged with the diagnosis of "Patent Ductus Arteriosus. Subacute Bacterial Endocarditis."*

*The author is indebted to Dr. Louis Greenstein, of Brooklyn, N. Y., for information concerning the details of the patient's illness prior to operation.

Examination.—On admission to Beth Israel Hospital, the patient appeared not only very acutely, but also chronically, ill. The temperature was 103.2° F., the pulse rate, 114, and the respiratory rate, 24. She was septic, dyspneic, cachectic, pale, and perspired profusely (Fig. 2).

The heart was slightly enlarged. The apex beat was felt immediately outside the midclavicular line in the fifth intercostal space, and was forceful and heaving. In the second intercostal space, 2 or 3 cm. to the left of the sternal border, a systolic thrill was present. A continuous machinery murmur, which was louder in systole than in diastole, was heard in the same area. The pulmonic second sound was greatly accentuated. The machinery murmur was transmitted upward as far as the first rib, and downward to the fourth rib medially. It was audible as far as the left sternal border, and laterally to the midclavicular line.



Fig. 2.—Patient on admission to hospital.

The blood pressure was 122/46-0. After resistive exercise of the leg (modified Bohn test), the blood pressure was 144/38-0. Examination of the lungs revealed medium-sized râles at the left base. The area of splenic dullness was increased. No petechiae were noted, and the remainder of the physical examination failed to disclose anything significant.

Laboratory Data.—A teleroentgenogram revealed marked enlargement of the left ventricle and pulmonary conus. A moderate sized area of infiltration, caused by pulmonary infarction, was noted adjacent to the left cardiac border. Moderate pulmonary vascular congestion was present (Fig. 3). Kymographic examination revealed marked pulsation of the pulmonary artery. The four lead electrocardiogram revealed slight right axis deviation, a small, inverted T₁, and a large, inverted T₂. The phonocardiogram disclosed a continuous murmur, systolic and diastolic, of maximum intensity over the second intercostal space, 2 cm. beyond the left sternal border. The circulation time was normal. The urine was normal. The blood contained 3,590,000 erythrocytes per cubic millimeter, and the hemoglobin content was 55 per

cent. The leucocyte count was unaltered. The erythrocyte sedimentation rate was 28 mm. in 45 minutes. The Wassermann, Kline, and Kahn tests gave negative results. A blood culture, taken on the day of admission, revealed 70 colonies of *Streptococcus viridans* per cubic centimeter after 48 hours' incubation. Because of the above observations, the admission diagnosis of patency of the ductus arteriosus, with superimposed, subacute, *Streptococcus viridans* endarteritis, was confirmed.

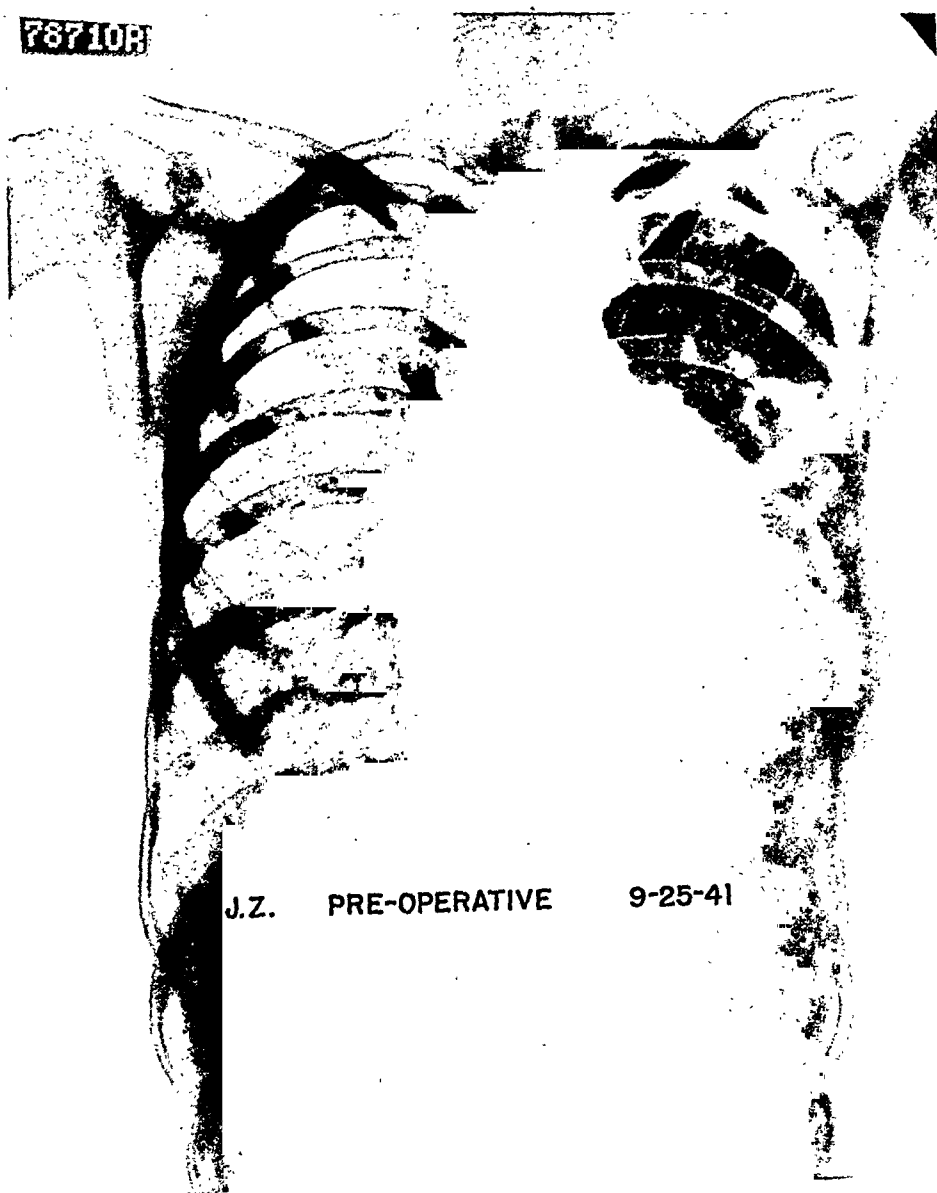
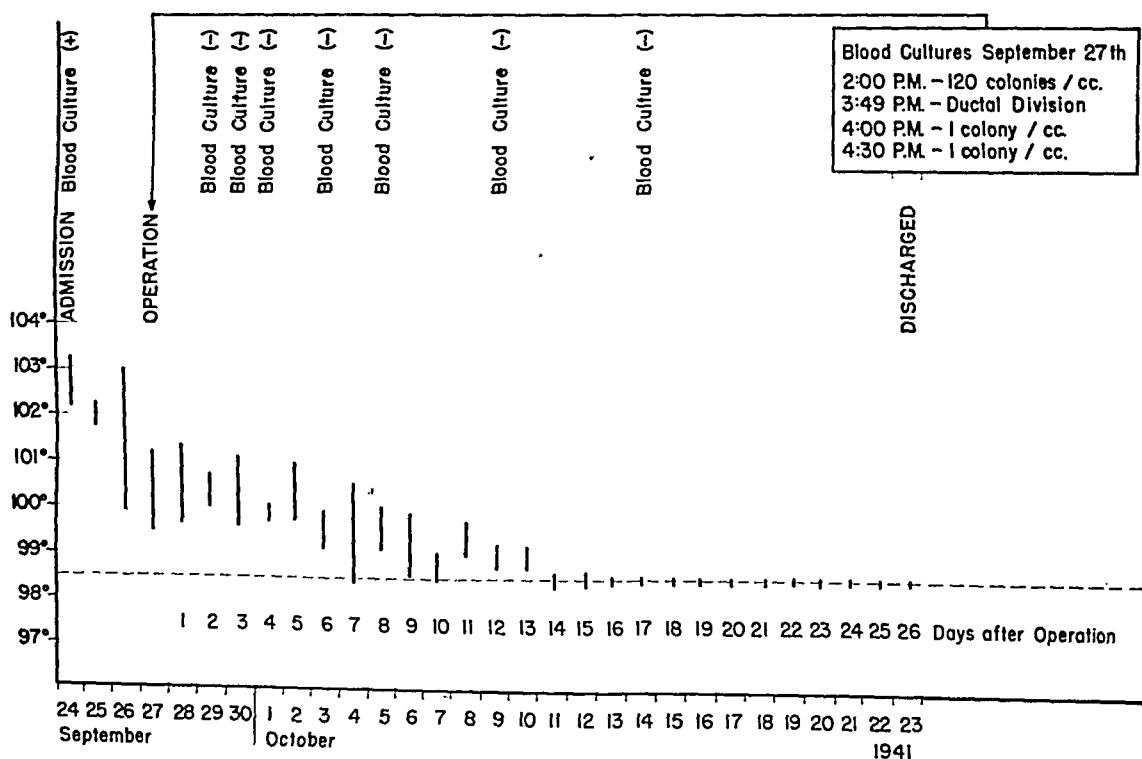


Fig. 3.—Roentgenogram taken on admission. Note the great increase in the size of the heart and the presence of a pulmonary infarct immediately adjacent to the left cardiac border.

It was decided to subject the patient to operation without delay, for the following reasons: (1) the septic, progressively unfavorable course, (2) the failure to respond to prolonged and intensive chemotherapy prior to admission to the hospital, (3) the increasing circulatory involvement, as indicated by the progressive cardiac enlargement, the development of right axis deviation, and the increasing pulse pressure, (4) the persistently positive blood cultures, (5) the development of pulmonary infarction, and (6) the absence of evidence of other associated congenital cardiac

defects or active valvular lesions. Although the risk of operation appeared great, it also seemed that continuation of conservative therapy would almost inevitably lead to a fatal outcome in the near future.

Operation.—On September 27, 1941, three days after admission, operation was performed (by A. S. W. T.) under cyclopropane-oxygen-ether anaesthesia by a technique previously described.¹³ The essential operative findings were as follows: (1) widespread adhesions of the left upper lobe of the lung to the pericardium, mediastinum, and interior of the thorax, anteriorly and laterally, (2) an area of pulmonary infarction, measuring roughly 3 by 3 inches, in the anterior axillary portion of the upper lobe, adjacent to the pericardium, (3) marked cardiac enlargement, (4) a visible tremor and palpable thrill over the base of the heart and pulmonary artery, (5) a greatly dilated pulmonary artery ($1\frac{1}{4}$ inch in diameter), the tenseness of which approximated that of the aorta, (6) intense edema of the mediastinal pleura ($1\frac{1}{4}$ inch thick), and edematous, inflamed lymph nodes at the local site; and (7) an inflamed, indurated ductus arteriosus, approximately $\frac{1}{2}$ inch long and $\frac{1}{2}$ inch in diameter, which was markedly adherent to the surrounding structures, and especially to the upper end of the trunk and right branch of the pulmonary artery.



J.Z. Case No. 7

NO CHEMOTHERAPY ADMINISTERED POST-OPERATIVELY

Fig. 4.—Clinical chart. Note temperature and blood cultures before and after operation. (Chemotherapy administered without effect, prior to admission to hospital. Chemotherapy not administered, after admission, either pre- or postoperatively.)

Slight bleeding was encountered as the final stage of dissection of the ductus was being completed, and therefore the ductus was doubly clamped and divided completely.* The two clamped ends then were ligated individually with heavy silk. The blood pressure after ligation rose from 118/40 to 150/80.

*The particular operation performed in this case and in Case 1¹ represent the only two such procedures to be reported in the literature thus far.

A blood culture taken during operation, before the ductus was ligated, later was reported to contain 120 colonies of *Streptococcus viridans* per c.c. after 48 hours of incubation. The first postoperative blood culture was taken in the operating room, eleven minutes after actual division of the ductus. This was an arterial specimen (taken from the radial artery). After forty-eight hours of incubation, it contained only one colony of *Streptococcus viridans* per c.c. The second postoperative culture was taken thirty minutes later; it also contained one colony per c.c., after forty-eight hours of incubation.

Postoperative Course.—The postoperative course was astonishingly uneventful. The cardiac murmur disappeared at once, and the fever subsided progressively (Fig. 4). Concomitantly, the toxic appearance vanished, and a sense of well-being returned. After a transfusion, the hemoglobin content of the blood rose from 55 per cent to 70 per cent. The patient was permitted out of bed on the ninth postoperative day and regained strength rapidly. The blood pressure quickly became stabilized at a level of approximately 130/90; and, during the postoperative hospital stay, the weight rose from 85 to 92½ pounds.



Fig. 5.—Patient seven and one-half months after operation. Note marked improvement in general physical condition and state of nutrition.

In addition to the two blood cultures which were taken in the operating room after division of the ductus, cultures were taken on the second, third, fourth, sixth, eighth, twelfth, and seventeenth postoperative days. All remained sterile throughout fourteen days of incubation. No chemotherapy was administered at any time.

At the time of discharge, on the twenty-sixth postoperative day, the patient was in excellent general physical condition, her circulatory status was normal, and all clinical and laboratory evidence of subacute *Streptococcus viridans* infection had disappeared. Thirty-six weeks have elapsed since operation. During this period the patient has remained entirely free of symptoms referable to infection and circulatory failure and has gained forty-six pounds in weight (Fig. 5). According to her

parents, she is in better physical condition than at any time since birth. The heart has diminished considerably in size and the previous site of the pulmonary infarct is identifiable only by a small residual shadow (Fig. 6).

Summary.—A schoolgirl, aged 18 years, had a patent ductus arteriosus complicated by mild circulatory insufficiency. Subsequently, subacute *Streptococcus viridans* endarteritis developed. She was admitted to a hospital, where intensive chemotherapy for five weeks failed to result in improvement. While she was there, the circulatory involvement increased.



Fig. 6.—Roentgenogram of chest seven months after operation. Note reduction in size of heart. Pulmonic conus is less prominent. Faint shadow adjacent to left cardiac border represents the remains of the previous pulmonary infarct. Pulmonary vascular congestion is still present.

When first observed by the author, she was acutely ill, septic, anemic, and cachectic. Left-sided pulmonary infarction was present. The blood contained as many as 120 colonies of *Streptococcus viridans* per c.c. Although she appeared to be an unusually poor surgical risk, operation was performed promptly in the hope of eliminating infection.

The surgical procedure consisted of division and double ligation of the ductus arteriosus. The blood cultures became sterile promptly after operation, without the use of chemotherapy.

The postoperative course, which was remarkably uneventful, was characterized by rapid disappearance of all manifestations of infection and circulatory involvement. Thirty-six weeks have elapsed since operation and the patient remains entirely well.

SUMMARY

Subacute *Streptococcus viridans* endarteritis may involve a patent ductus arteriosus at any age.

Under conservative therapy, the disease has proved to be almost invariably fatal.

In the early stages of infection, vegetations are likely to remain confined to the ductus and pulmonary artery. In the latter stages of infection, or even in the early stages of severe infection, vegetations may spread to the cardiac valves or into the aorta. Aortic spread seems to occur chiefly in cases in which the ductus is short.

Eleven patients who had patency of the ductus arteriosus complicated by subacute *Streptococcus viridans* endarteritis were subjected to operation consisting of ligation (9 cases) or division (2 cases) of the ductus. Nine patients survived the operation; two died of operative hemorrhage.

Of the nine survivors, six recovered from infection without benefit of chemotherapy. The remaining three patients did not recover from infection, despite chemotherapy.

Of the six patients who recovered, none presented evidence of pre-operative spread of vegetations to the cardiac valves or aorta. They have been followed for periods of three to twenty-nine months; all are well and have had repeatedly negative blood cultures.

Of the three patients who failed to recover from the infection, two presented evidence of vegetative valvular lesions prior to operation. The third was assumed to have vegetations at the aortic end of the ductus. One died of subacute *Streptococcus viridans* endarteritis approximately eight months after operation. The other two are unimproved fourteen and sixteen weeks, respectively, after operation.

Various aspects of infection of a patent ductus arteriosus which have a bearing upon the results of operative treatment are discussed.

A case to illustrate the safety of operating upon even very ill patients is presented.

CONCLUSIONS

Ligation or division of the ductus, if performed before vegetations have spread to the cardiac valves or aorta, is an effective and safe method of treating subacute *Streptococcus viridans* endarteritis involving a patent ductus arteriosus.

In view of the fact that conservative therapy seldom proves curative, and that the rapidity of spread of vegetations is unpredictable, operation should be undertaken as soon as the diagnosis of superimposed infection has been established.

ADDENDUM

Since preparing this paper, another patient with an infected patent ductus arteriosus has been operated upon. In view of the nature of the infecting organism (*Staphylococcus aureus*) and the severity of the clinical manifestations, the case was considered one of acute, rather than subacute, bacterial endarteritis. The total duration of infection prior to operation was eleven days. Ligation of the ductus, followed by chemotherapy and the administration of Meleney's bacteriophage, proved effective. Thus the series now consists of twelve operative cases, among which there were seven recoveries, three failures, and two operative deaths.

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DISCUSSION ON "PATENCY OF THE DUCTUS ARTERIOSUS IN ADULTS," BY DRS. ANCEL KEYS AND M. J. SHAPIRO, MINNEAPOLIS, MINN., AND "THE RESULTS OF SURGICAL TREATMENT OF PATENCY OF THE DUCTUS ARTERIOSUS COMPLICATED BY SUBACUTE BACTERIAL ENDARTERITIS," BY DR. ARTHUR S. W.

TOUROFF, NEW YORK, N. Y.

DR. ROBERT L. LEVY, New York.—The experiences which Dr. Touroff has related are, indeed, exciting, and represent another forward step in the surgical treatment of heart disease. At the Presbyterian Hospital in New York, Dr. George Humphreys has

ligated a patent ductus in twelve patients and has kindly placed his data at my disposal. There has been no operative mortality. Five of the group showed bacterial invasion of the blood stream. It is to these five patients that I shall refer briefly.

Three of them are cured. The first patient was a child, 12 years old, with staphylococcus sepsis complicating previous ligation of the ductus, which had reopened. The second patient was also a 12-year-old child who developed *Streptococcus viridans* septicemia after measles. In both cases, adequate treatment with one of the sulfonamide drugs was ineffectual. The third patient was a 30-year-old woman who had had a *Streptococcus viridans* infection for several months; the blood had been rendered sterile by chemotherapy shortly before operation. The fourth case was that of a 42-year-old man with an associated septal defect. Ligation was done only last week, so that the result is still uncertain. The invading organism was a nonhemolytic streptococcus.

The fifth patient died of *Streptococcus viridans* sepsis eight weeks after operation. Multiple lesions were suspected before ligation was performed, both because of the physical signs and the occurrence of peripheral emboli. At autopsy, the ductus, which had been apparently patent at operation, was found to be obliterated, and neither at the pulmonic nor at the aortic end were there signs of infection. Large clusters of vegetations clung to a defect in the interventricular septum and others were present on the mitral, aortic, and pulmonic valves. There were infarcts in the spleen, kidneys, and lungs.

In view of the poor prognosis and the small operative risk, it seems fair to conclude that, in the presence of patency of the ductus arteriosus combined with bacterial sepsis, ligation should be carried out. This may be done even when a septal defect or a valvular lesion is suspected, with the hope that the focus of infection lies in the ductus. Operation is sometimes curative when preliminary chemotherapy has failed to sterilize the blood. The occurrence of peripheral emboli, however, lessens the likelihood of a successful result.

DR. M. J. SHAPIRO, Minneapolis.—Three years ago, before this Association, I presented clinical observations in seventeen cases of patency of the ductus arteriosus. These patients had been followed over a period of years. Later we presented observations in twenty-six cases. It was pointed out then that none of our patients had died and none had developed subacute bacterial endarteritis or congestive failure. Three of these patients were later referred for ligation of the ductus. The result in the first two cases was poor. In the first instance, the vessel which was tied was not the patent ductus, for no change occurred after ligation. The second patient died as result of rupture of the duct at operation. In the third case the operation was completely successful.

As a result of this experience, considerable doubt arose as to the advisability of surgical treatment for the remainder of our patients. We, therefore, decided to delay further surgical interference until we could complete two additional studies. The paper just presented by Dr. Keys on patency of the ductus arteriosus in the adult is one of the studies. The other concerns itself with the results of ligation in all patients operated on up to the present time. We have analyzed the available data in all such cases. The results of this analysis are summarized in a slide which I should like to present at this time. Briefly, this slide shows that twenty-six surgeons have operated upon one hundred thirty-seven patients with patency of the ductus arteriosus. One hundred four of these patients had no infection, and thirty-three had subacute bacterial endarteritis. Of the one hundred four uncomplicated cases, the results were completely successful in seventy-eight. In fourteen instances, the continuous murmur persisted after ligation. Six patients died as a result of rupture of the duct at operation. Two patients developed subacute bacterial endarteritis after ligation. Death resulted in one case as a result of wound infection, and, in one case, nothing could be done because there was a direct arteriovenous communication. In three in-

stances a vessel other than the ductus was ligated. A total of nine patients died as a result of operation, which makes the mortality rate less than 10 per cent. Of the thirty-three cases complicated by subacute bacterial endarteritis, operation resulted in complete success in twenty; that is, the temperature returned to normal, the murmur disappeared, and the patient regained normal health. These patients have not been followed long enough to be sure that they are definitely cured. Five died as a result of rupture of the duct at operation, and, in eight instances, the fever persisted in spite of successful ligation. It is a remarkable fact that, in this entire series of one hundred thirty-seven patients, there were only two errors in diagnosis. It appears, therefore, that, in the hands of well-trained surgeons, ligation of the ductus arteriosus can be performed with less than 10 per cent mortality. This rate will certainly decrease as more experience is gained. It seems likely, too, that most patients with patency of the ductus arteriosus complicated by subacute bacterial endarteritis can be cured by surgical interference, especially if the operation is done early. In spite of these very favorable results, we still feel that only those patients on whom a diagnosis of uncomplicated patency of the ductus arteriosus can be made should be operated upon, and then only after definite evidence of early cardiac enlargement or cardiac embarrassment is present. Our point of view may become less conservative after a number of years of follow-up study of the patients who have been operated upon.

I should like to take this opportunity to disagree with Dr. Levy with regard to operating upon patients with patency of the ductus arteriosus complicated by other congenital heart lesions. I do not believe that surgical treatment should be attempted in any case in which there is the slightest doubt about the diagnosis. Simple, uncomplicated patency of the ductus arteriosus, as an isolated lesion, can be diagnosed correctly, and, in my opinion, in only those cases should the ductus be ligated. No patient with cyanosis or with an electrocardiogram which shows right axis deviation should be operated upon. There is good evidence that isolated patency of the ductus arteriosus is not a congenital cardiac lesion at all. It is not a developmental defect in the same sense that all other congenital heart lesions are. It is to be noted that all of us are born with a patent ductus arteriosus.

DR. PAUL D. WHITE, Boston.—Some of you will have known of Dr. Bourne's paper, published in *Lancet*, October, 1941, concerning recovery in two cases after ligation and chemotherapy of bacterial invasion of a patent ductus arteriosus. You will be interested in the latest word that came from him, a few days ago, saying that he now has five recovered patients out of six treated by this procedure—combination of ligation and chemotherapy—and that the seventh is about to be operated upon.

I would like also to add a conservative note about the incidence of bacterial endarteritis in patency of the ductus arteriosus. It is really a thought of John Hubbard, a colleague of mine in Boston, who has been associated with Dr. Gross during and since the period of the early ductus operations. He believes, and I am in agreement with him in this respect, that we do not yet have accurate statistics about the incidence of subacute endarteritis in patency of the ductus arteriosus. He thinks that the statistics are weighted now by the fact that the patients who have the infection attract more attention, are more likely to be in hospitals, and are more likely to have autopsies performed on them. We still need fuller and more accurate statistical studies of the incidence of bacterial endarteritis complicating patency of the ductus arteriosus.

DR. MAX WILSON, New York.—I think what Dr. White has said is very important. We have not had adequate statistics on the natural risk for a patient with a patent ductus.

In a paper that is now in press, we have attempted to obtain such data. Over a period of twenty-five years we have observed about 132 children who had some congenital cardiac abnormality. Of these, 32 were considered to have a patent ductus.

Upon analyzing the life expectancy, we found that the risk of dying in any year in the first three decades was about 1 chance in 200. Comparing that with the last mortality risk from ligation quoted by Gross as 1 chance in 10, at the moment I would hesitate in advising operation on a well child.

But we must have more statistics. It must be recognized that the present erroneous impression of the risk of subacute bacterial endarteritis in patients with patency of the ductus is based entirely on reported deaths. The living persons with patency of the ductus are not included in those rates.

DR. B. S. OPPENHEIMER, New York.—A few years ago I think most physicians were not very enthusiastic about surgical treatment of heart disease, but since then there are two conditions in which operation seems to be indicated. One is chronic constrictive pericarditis, to which Dr. White has contributed so notably, and the second is patency of the ductus arteriosus, especially when the patient has bacterial endarteritis and positive blood cultures.

Through the courtesy of Dr. Touroff, I saw five of the seven patients whom he reported, and two points struck me particularly. The first was that one of the patients, after successful ligation, had a machinery murmur which was very loud and perfectly evident to everybody. The second point was the rapidity with which the blood was cleared of the *Streptococcus viridans*. That was very striking.

We have had discussions about these points, and, the last time I asked Dr. Touroff about the latter, he thought that the lungs filtered out the *Streptococcus viridans* and this cleared the blood rapidly. In one case the bacteria disappeared from the peripheral blood stream a few minutes after ligation.

I should like to ask him how he explains the persistence of the machinery murmur and the very rapid disappearance of the bacteria from the blood.

In considering the statistics of recovery from *Streptococcus viridans* infections of the heart or arteries, one should remember that the prognosis of such infections is better when the infection is superimposed upon a congenital anomaly than when it involves an acquired lesion.

DR. EMANUEL LIBMAN, New York.—As you realize, it is a notable result that has been achieved by Dr. Touroff.

The whole development of this subject is very interesting. First, great credit is due to Dr. Maude Abbott. Few realize how great her contribution has been. She will become a greater and greater figure as time goes on. When I was first questioned by Dr. Touroff, I applied to Dr. Abbott for certain data. Some had an idea that Dr. Abbott's search for statistical data would be without real value. Actually, when I wrote for information on certain essential points, she promptly sent all the statistical data that were very much needed. It almost looked as if she had made her studies with this operative procedure in mind.

We must give credit to Dr. Robert Gross, who devised the original operative procedure and performed it successfully in cases in which no infection had occurred by way of the ductus.

Then comes the work of Dr. Touroff, who had great enterprise and ingenuity. It was very courageous to attempt to carry out ligation of the ductus in the presence of infection. This was particularly true because in two patients without infection, on whom ligation was done by others, infection of the ductus and pulmonary artery resulted.

Helpful in the advancement of the work have been the diotrast studies which were first made by Robb and Steinberg (I.), and later by Sussman, Steinberg (M. F.), and Grishman. Such studies are absolutely essential in some cases. We have reason to believe that, in the presence of certain congenital cardiac defects, ligation of the ductus may be harmful to the circulation.

My own calculations would seem to indicate that an open ductus is even more frequently present than Dr. Touroff has indicated.

When I encouraged Dr. Touroff to proceed with his operative studies, I did not do so for empirical reasons. Subacute bacterial pulmonary arteritis depends for its development on the infective agent, tension, irregularities of the wall that may be present as a result of tension and, perhaps, thrombi on such irregularities, and the presence of oxygenated blood. We know how little tendency there is for the valves on the right side of the heart to become the seat of subacute bacterial endocarditis. It is believed that this is because of the presence of venous blood and lower pressure. When the ductus is ligated or resected, the high pressure is reduced, and the supply of arterial blood is stopped.

The blood cultures become negative, I believe, because of the great diminution in the force of the current on the vegetations. It must be remembered that, with any source of a bacteremia, even if the focus is radically removed, a few stray bacteria may remain in the blood for a few days. Then one is likely to find them only in cultures made in fluid media.

Dr. Oppenheimer brought up the question as to the mechanism of the murmur in these cases of patency of the ductus. After Dr. Touroff had ligated and sectioned the ductus in the first case, a continuous murmur was still heard, although less marked. When he pressed on the pulmonary artery, the murmur disappeared. We must suspect that the continuous murmur is caused by the passage of blood at high pressure to a dilated pulmonary artery, without tense walls.

DR. J. W. WILCE, Columbus.—I have never seen or heard of a case such as I want to show you.

This slide shows a team after they had won a championship. One of these boys had patency of the ductus arteriosus. He played for two years with chronically infected tonsils and a patent ductus arteriosus. When he came in on a matter of consultation the third year, it was decided that he should have his tonsils removed, wait six weeks, and after that try half-time work and stop even modified play in case suggestive symptoms were noted.

I am postulating that the ductus shown in the slide is a pretty large and long one. It is a "silent" one, but when one investigates it in the left oblique position, a pulsating connection between the aorta and pulmonary artery is seen. It is possible that the increase in stroke volume that comes with sports was the cause of that dilatation of the patent ductus arteriosus.

DR. SAMUEL E. LEVINE, Boston.—As I see it, there are two therapeutic problems that we are working with: ligation for subacute bacterial endarteritis involving a patent ductus, and ligation of a noninfected ductus.

There cannot be very much argument about the first. We know about the mortality rate of subacute bacterial endarteritis involving a patent ductus. It is extremely high, and the operative risk is becoming less and less. In Boston, Dr. Gross had no deaths in the last thirty cases; other surgeons will do likewise with a little experience and care, perhaps not so much experience, as anatomic knowledge. It is imperative, however, that we make the diagnosis early. We can almost guarantee a cure if the diagnosis is correct and made early, and if we do not wait three months for chemotherapy to be tried. So I don't see that there can be any question about the value of the operation in subacute bacterial endarteritis.

The other question is entirely an open one. It is important to remember what we heard this morning, namely, that the average age at death in fifty or sixty cases of uncomplicated patency of the ductus was only 35 years. Those patients were over 17 years old when first seen; people who are well at 17 years are expected to live to 60 or 70 years. This group lived only to 35 years, and I do not know that we can make any prediction at the age of 18 or 20 years as to which one person is going

to develop subacute endarteritis. Therefore, we must try to find out whether the operation prevents subacute bacterial endarteritis. If so, the mortality risk of surgical treatment is a great deal better than letting the person live his life expectancy, which averages 35 years. The question we have to keep in mind is: Will the operation prevent subacute bacterial endarteritis? It certainly will prevent subsequent heart failure if that is the only lesion.

DR. ARTHUR S. W. TOUROFF, New York.—I am happy to hear from Dr. Levy and Dr. White that the work which I have presented has already been confirmed by other investigators.

In answer to Dr. White and Dr. Wilson, I would like to emphasize that my presentation deals only with the treatment of patency of the ductus arteriosus which is already complicated by subacute bacterial endarteritis. Under the circumstances, the actual incidence of subacute bacterial endarteritis as a complication of patency of the ductus does not concern us here, for the reason that we are not discussing the value of operation as a prophylactic procedure in the prevention of infection. To the patient who has already developed subacute bacterial endarteritis, the incidence of this complication is 100 per cent. Thus, we are not operating to prevent infection, but are treating patients who already have infection.

By way of discussion of Dr. Wilson's statements, if a group of normal children have a certain life expectancy, it seems logical to assume that those with a patent ductus who are threatened by cardiac failure and subacute bacterial endarteritis have a shorter expectancy of life. In this connection I would again like to point out that cardiac failure may develop late in life, and that subacute bacterial endarteritis occurs more commonly in adults than in children. Thus if we use the age criterion of Drs. Keys and Shapiro, we find that infection occurred during childhood in only one of our eleven cases.

In answer to Dr. Oppenheimer, it is to be emphasized that a continuous machinery murmur persisted after operation only in the first case. Since the ductus was divided completely, recanalization could not have occurred. When the case was reported originally, I drew attention to the fact that, during operation, the murmur became less intense, but did not disappear until the pulmonary artery was temporarily compressed. This seemed to indicate that the murmur was generated within the latter vessel. Several of the other patients had residual, soft, systolic murmurs which are gradually becoming less intense.

Time does not permit discussion of the mechanism of recovery, but I believe that operation is effectual chiefly because it corrects certain abnormal mechanical factors. This subject will be presented in a separate paper.

In conclusion, I urge that operation be performed promptly upon all patients who have developed infection.

DR. ANCEL KEYS, Minneapolis.—In connection with the recurrence or persistence of a murmur in some cases after ligation, I should like to point out that we have evidence that there may be an open ductus with no murmur, but there is no proof that we may have a murmur with the ductus closed. Duroziez, in 1862, reported a case of patency of the ductus arteriosus (diagnosis substantiated at autopsy), in which there was no murmur of any kind, and we have recently had a similar case, likewise with autopsy. In both of these instances the pulmonary artery was enlarged, so that we should have expected murmurs if the murmur of a patent ductus is primarily a result of pulmonary enlargement. Further, we know that, in at least one instance in which a murmur recurred after ligation, there had been, in fact, re-establishment of communication between the aorta and pulmonary artery. Unless some really valid evidence to the contrary is presented, I believe we must assume that persistence or recurrence of the murmur after attempted ligation indicates persistence or recurrence of the aorta-pulmonary artery communication.

A PHYSIOLOGIC DEFINITION OF ACUTE CONGESTIVE HEART MUSCLE FAILURE

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THERE is urgent need for an accurate quantitative definition of acute congestive heart muscle failure in physiologic terms. Such a definition should contain magnitudes which are not only capable of measurement in animal experiments, but which may be fairly accurately ascertained in measurements on patients with heart failure before and after treatment. In this paper we shall prove through animal experiments that decreased mechanical efficiency* is the basic factor in acute congestive heart failure. Papers in which this viewpoint will be established by investigations already carried out on man will appear shortly.

In 1912, Knowlton and Starling¹ devised the heart-lung preparation, and, in making use of this preparation, they showed that the ability of the mammalian heart to do work is a function of the diastolic length of the heart muscle fibers, or diastolic volume. In other words, if the heart is to do more work per beat either by increasing the stroke output or the mean blood pressure or both, it must dilate. In his Linaere Lecture on the law of the heart, Starling² stated that the failing heart produces less external work at a constant diastolic volume. Here we already have an accurate definition of heart muscle failure. This definition could be improved only if we knew the relationship of diastolic volume to total energy release per beat.†

Shortly after Starling devised his heart-lung preparation, Socin,³ in 1915, working in the physiologic laboratory of Magnus, in Utrecht, and Bijlsma and Roessingh,⁴ in 1922, carried out experimental investigations of acute cardiac weakness as produced by chloroform and chloral hydrate on the heart in a heart-lung preparation. They showed that chloroform and chloral hydrate produced dilatation of the heart, a decrease in cardiac output, and a decrease in average blood pressure, thus confirming Starling's statement that a failing heart does less work at a given diastolic volume. Starling tended to minimize the factor of increase in venous pressure when the heart dilates because of his conviction that it was the diastolic length of the heart muscle fibers that determined the work of the heart. On the other hand, every cardiologist

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*The ratio of work performed to the oxygen consumed in releasing energy from fuel materials is the mechanical efficiency of a machine.

†Total energy release = heat produced plus work performed.

is aware that the cardinal symptoms of heart failure, namely, dyspnea and dependent edema, are largely the result of a rise in venous pressure. On repeating these experiments, making use of chloroform and chloral hydrate to produce a hypodynamic heart muscle in heart-lung preparations, one of us (G. F.) noted that the venous pressure always rises at the same time that the heart dilates, and that the mean blood pressure could be held constant.* There is usually some decrease in cardiac output, also, but this may be very slight with moderate degrees of poisoning. In our teaching we then made dilatation and rise in venous pressure the criteria of heart failure.

Starling and Visscher⁵ showed that the oxygen consumption of the heart increased when the diastolic volume or length of the muscle fibers increased. Dechard and Visscher¹¹ found that the work of the turtle heart decreased during spontaneous failure when the diastolic volume, and, therefore, the oxygen consumption, were held constant. Peters and Visscher⁶ showed that the ratio of the work performed by the spontaneously failing heart to the oxygen consumption of that heart increased when ouabain and scillaren^B were added to the blood circulating in the heart-lung preparation. A little later, Visscher and Moe⁷ proved that a digitalis glycoside, digilanid C (cedilanid), also increases the mechanical efficiency of the spontaneously failing heart. The experiments of Starling, Visscher, Peters, and Moe make it appear that a decrease in mechanical efficiency is the most likely cause of acute heart failure.

A search through the literature unearthed only one paper (with the exception of the papers from Visscher's laboratory, quoted above) in which an attempt was made to measure the diastolic size of the heart, the venous pressure, and the mechanical efficiency of the heart during spontaneous failure. In 1938, Katz and Mendlowitz⁸ published an analysis of spontaneous heart failure in the isolated heart circuit. They measured the diastolic size of the heart by means of either calipers or an oncometer. By obtaining arterial blood samples from the outflow system of the left side of the heart and venous blood from a glass cannula passed into the coronary sinus, they assumed they could calculate the oxygen consumption of the heart. In the summary of their paper, they stated that with their preparation it was possible to permit failure to occur with little or no change in total diastolic volume. They found that under these circumstances there was a progressive decrease in the work and oxygen consumption of the heart, and little change in its mechanical efficiency. They concluded that "when the work of the heart was kept constant, no change in oxygen consumption or mechanical efficiency occurred, despite a progressive increase in the diastolic volume and the left auricular pressure." They also concluded that failure of a heart chamber is caused by an increase in load or decrease in contractile power, or both, of such a degree that the chamber begins to fail to do the

*Unpublished experiments.

work imposed upon it by the load. They also state as a conclusion "that loss of contractile power is manifested by a reduction in total energy release, and hence work at a given diastolic volume and (except terminally) not by a decrease with which the liberated energy is utilized for mechanical work." The work of Katz and Mendlowitz cannot be considered as proving their conclusion because their measurements of oxygen consumption did not take into account the oxygen consumption of the blood that returned to the right side of the heart via Thebesian channels; it has been shown that the oxygen content of this blood may differ very greatly from that of the blood in the coronary sinus.⁹ Moreover, there is a discrepancy in their conclusions. They speak of heart failure in conjunction with little or no change in total diastolic volume in one statement, and, in another, they mention a progressive increase in the diastolic volume. Their one curve showing diastolic volume indicates a progressive increase in the volume. Katz and Mendlowitz state in their paper that it is apparent that loss of mechanical efficiency is not an essential factor in heart failure, and that such a loss does not occur except as a terminal event. We will show later that this statement is not true.

Since one of the poisons with which we did our work was diphtheria toxin, we wish to review the work of Witt, Lindner, and Katz,¹⁰ who studied the effects of acute experimental poisoning of the heart with diphtheria toxin. They made use of the intact dog, so that their work not only shows the effect of diphtheria toxin upon the myocardium, but also upon the peripheral circulation. Under the conditions of their experiments, the stroke volume declined. They also state that there was distention of the heart. Their two published curves show at times a rise, and, at other times, a decrease in the diastolic pressure in the left ventricle (venous pressure) during the poisoning. In our opinion, this is because they were dealing with a combination of heart failure and peripheral vascular failure. We can find no measurements of stroke or minute output, and no quantitative data on changes in the diastolic volume of the heart. Among other things, they observed various cardiac arrhythmias which could have been produced by diphtheria toxin. Because of the complications in the experiments of Witt, Lindner, and Katz, we do not believe that this work can be accepted as the final word regarding the effect of diphtheria toxin on the myocardium itself.

Our search of the literature convinced us that there was a place for renewed investigation of the physiologic factors of diastolic volume, mechanical efficiency, venous pressure, cardiac output, and blood pressure when the heart is made hypodynamic by the administration of cardiac poisons.

An experiment to ascertain the effect of cardiac poisons on the function of the mammalian heart muscle should be carried out only on the isolated heart-lung preparation or an isolated heart with a mechanical

oxygenator taking over the function of the lung, because, otherwise, peripheral vascular factors will mask or complicate the results of the heart muscle failure. Because of our many years of experience with the Starling heart-lung preparation, we selected this method. Later we added the Vischer oxygen consumption apparatus. As cardiac poisons, we selected chloral hydrate, chloroform, diphtheria toxin, alcohol, and potassium chloride. Fig. 1 is a schema of the heart-lung preparation as used by us. It is essentially a heart connected to the pulmonary circulation with the lungs intact, with an artificial resistance, which can be varied to suit the desires of the experimenter, inserted into the arterial circulation. This circulation consists of a glass cannula in the brachio-

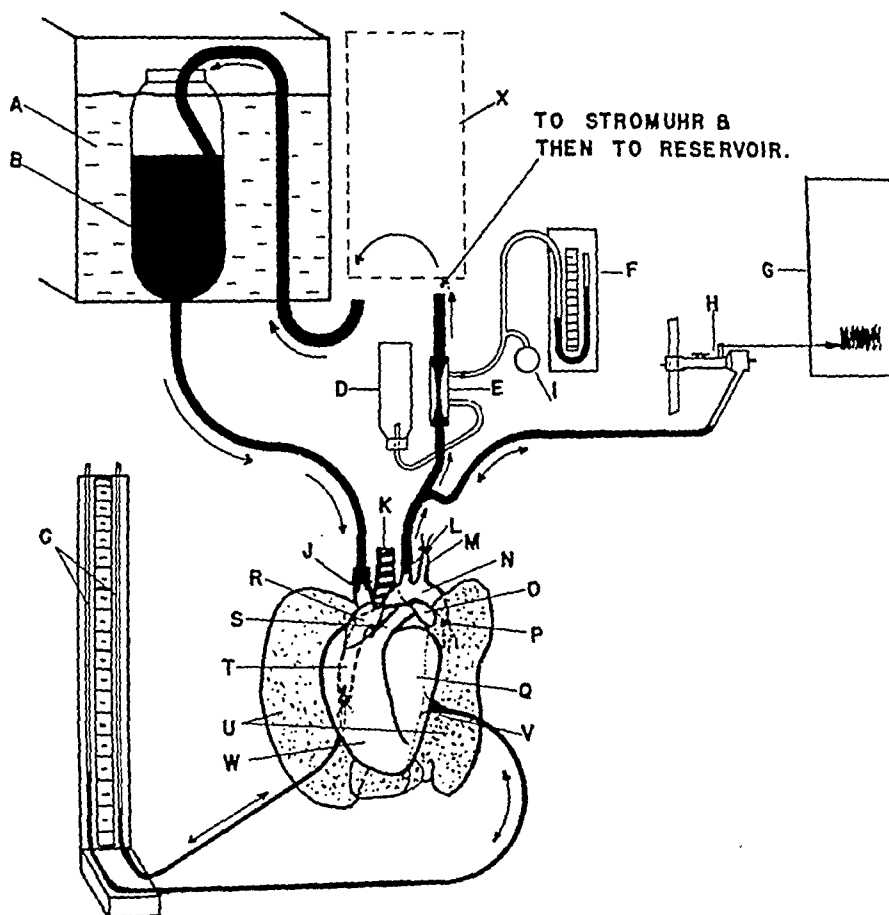


Fig. 1.—A, Constant temperature bath; B, blood reservoir; C, venous pressure manometer; D, bottle used as air cushion for peripheral resistance chamber; E, peripheral resistance chamber; F, mercury manometer; G, kymograph; H, Straub blood pressure manometer; I, pressure bulb; J, superior vena cava and cannula; K, trachea; L, brachiocephalic artery and cannula; M, ligated subclavian artery; N, arch of aorta; O, left auricle; P, ligated aortic arch; Q, left ventricle; R, right auricle; S, pulmonary artery; T, inferior vena cava and cannula; U, lungs; V, small cannulated pulmonary vein; W, right ventricle; X, position where stromuhr stands.

cephalic artery of the dog and a series of glass and rubber tubes carrying the blood pumped out of the heart up to the venous reservoir, which is itself connected to the superior vena cava by rubber tubing and a glass cannula (Fig. 1). All of the branches of the root of the aorta, except the brachiocephalic artery, are ligated, and the aorta itself is ligated just beyond the brachiocephalic artery. Thus the only part of

the systemic circulation which remains intact is the root of the aorta. The lungs are ventilated by means of a pump, so that the heart-lung preparation is kept well oxygenated. In the heart-lung preparation as we used it for this experiment, one water manometer was connected to the inferior vena cava in order to measure the right auricular pressure, and another was connected with a branch of the pulmonary vein in order to measure the left auricular pressure. A cardiometer, fitted around the auriculoventricular groove, was connected to a large tambour in order to record changes in the diastolic and systolic volume of the ventricles. At the beginning and end of each experiment the cardiometer was calibrated by noting the excursions of the tambour level after injections of 20 c.c. quantities of air into the cardiometer system. It was thus possible to measure dilatation of the ventricles in cubic centimeters. A cannula, connected to a Straub membrane manometer, was inserted into the arterial circulation near the brachiocephalic artery, and a Stolnykow stromuhr for measuring minute output of the heart was connected to the arterial circulation just beyond the artificial resistance. The venous reservoir was kept at constant temperature by a water bath which was heated and stirred electrically. A device connected to the heating element kept the temperature constant within 0.1° C. A screw clamp, connected to the rubber tubing leading from the venous reservoir to the cannula in the superior vena cava, regulated the rate of volume inflow into the right auricle.

It has been our experience that the artificial resistance keeps the arterial diastolic pressure nearly constant at the desired level throughout great changes in the conditions of the experiment. The systolic blood pressure varies with the stroke output of the heart. There is easy access to the venous reservoir, so that cardiac poisons or digitalis glycosides can be inserted readily. The minute volume is measured by observing the time (with a stop watch) required for the blood to flow from one mark on the stromuhr to another mark; the volume between the two marks is 50 c.c. The stop watch measures one-fifth of a second. The error of the measurement of minute volume is determined by this one-fifth second scale division. The rate of the heart is largely controlled by the temperature in this preparation, so that the heart rate remains constant over a large range of changes. Cardiac poisons may cause heart block, extrasystoles, and auricular fibrillation, all of which may alter the ventricular rate; otherwise the rate of the ventricles is constant.

When we measured oxygen consumption, we made use of the heart-lung preparation in the oxygen consumption apparatus, as devised by Dr. Visscher.⁶ In this case we used the apparatus in Dr. Visscher's laboratory and had the advantage of his advice, as well as that of Dr. Lorber, an assistant in his department. If proper precautions are taken, the results obtained with this apparatus are accurate. The clinician will note that this method of measuring oxygen consumption is an adapta-

tion of the one which he uses in estimating the basal metabolic rate; the adaptation is made to the trachea of the heart-lung preparation rather than to the mouth of the patient. A pump is inserted in the apparatus to keep the oxygen circulating into the lung during the inspiratory stroke and out of the lung and into the spirometer when the stroke of the pump is in the opposite direction. Fig. 2 is Dr. Visscher's schema of this apparatus. We will not go into a discussion of its accuracy; this has been done by Dr. Visscher, and a critical reader can look it up in his papers. Let it be said that the results obtained with this oxygen consumption apparatus have been checked with those obtained with an isolated heart and mechanical oxygenating apparatus and found to be accurate if the proper precautions are taken.

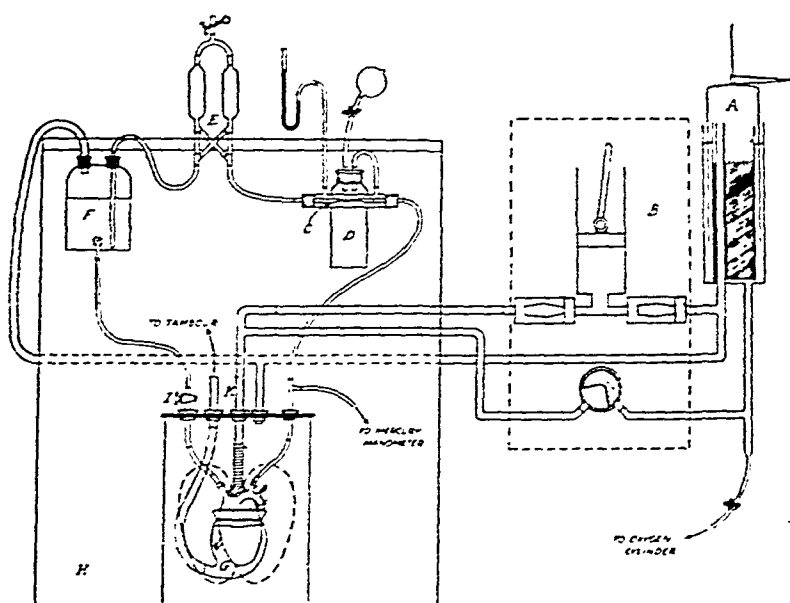


Fig. 1.—A, oxygen spirometer; B, respiration pump; C, artificial resistance; D, pressure bottle; E, Stromuhr; F, venous reservoir; G, cardiometer; H, constant temperature bath; I, stopcock for adjustment of venous return; K, tracheal cannula.

Fig. 2.—Schematic drawing of the Visscher heart-lung oxygen consumption apparatus. This is a photograph of Fig. 1 from the paper by Peters and Visscher, *The Energy Metabolism of the Heart in Failure and the Influence of Drugs Upon It*, AM. HEART J. 2: 273, 1936. Dr. Visscher's permission was obtained for the use of this figure.

In the course of this investigation we repeated the original experiments of Starling upon which the law of the heart was based. In Fig. 3 we show the effect of increasing the venous return to the heart. Starting with a volume flow of 50 c.c. in 11.2 seconds in the arterial system, or a minute volume of 270 c.c. per minute if we neglect the coronary flow, we observed that the venous pressure in the pulmonary vein on the left side was 3.3 cm., and, on the right side, or in the inferior vena cava, was 2.8 cm. of water. The blood pressure was 105/95. Now the inflow from the venous reservoir was increased by taking off some of the pressure on the clamp constricting the tube running from the reservoir to the superior vena cava. The flow immediately increased until 50 c.c. were injected from the left ventricle into the arterial system in 2.8 seconds,

which gave a minute output of 1070 c.c., neglecting the coronary flow. The blood pressure at this time was 117/91. The venous pressure went up on the left to 9.5 cm., and, on the right, to 8.7 cm. At the same time the heart dilated 25 c.c. in diastolic volume. The inflow from the venous reservoir was now decreased until it took 5.6 seconds to eject 50 c.c. from the left ventricle into the arterial system, giving a cardiac output of 535 c.c. per minute if we neglect coronary flow. The blood pressure at this time was 112/95. The venous pressure went down to 5.0 on the left and 4.5 on the right, and the dilatation of the heart receded 18 c.c.

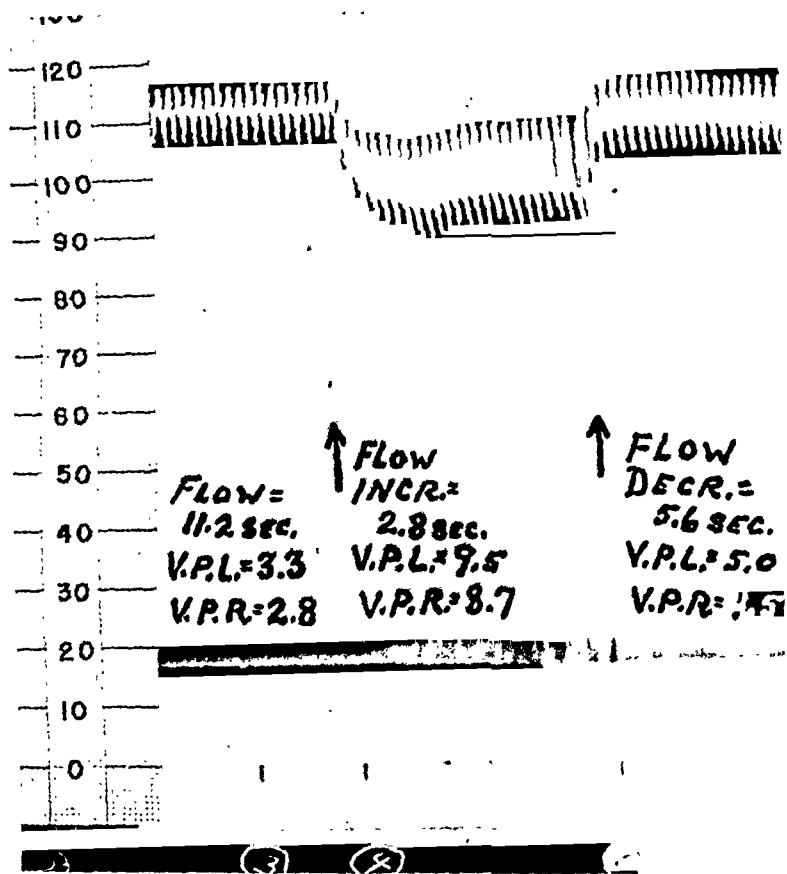


Fig. 3.—Influence of cardiac output on the diastolic volume of the heart and on the venous pressure. Top curve is cardiometer tracing, systole up, diastole down. Dilatation is represented by a downward displacement of the curve. Blood pressure curve (Straub manometer) below cardiometer tracing. "Flow" means the number of seconds during which 50 c.c. of blood flowed from the left ventricle into the aortic system, as measured in the flow meter. This amount is exclusive of the amount flowing into the coronary system. VPL = venous pressure on the left in cm. of water. VPR = venous pressure on the right in cm. of water. The dilatation of these ventricles was 25 c.c. in going from a minute flow of 270 c.c. to a minute flow of 1,070 c.c.

At the end of this experiment we tied off the two ventricles just beyond the cardiometer and measured their volume with the contained blood. This volume was 120 c.c. The weight of the ventricles without the blood was 97 grams. From data published in the thesis of Hymer L. Friedell, "The Estimation of the Size and Stroke Output of the Heart by Means of Roentgenkymography," submitted to the University of

Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy, as well as from data obtained by roentgenkymography on the hearts of two internes at the Minneapolis General Hospital, we calculated that the diastolic volume of the heart of a man 170 cm. in height and weighing 70 kilos is approximately 600 c.c. The diastolic volume of this average man's heart would increase by 125 c.c. under the same conditions that cause the 25 c.c. dilatation in our dog's heart, assuming that the diastolic volume of the auricles enlarges proportionately with that of the ventricles. From data obtained by roentgenkymography on the two internes' hearts we have calculated that the enlargement of

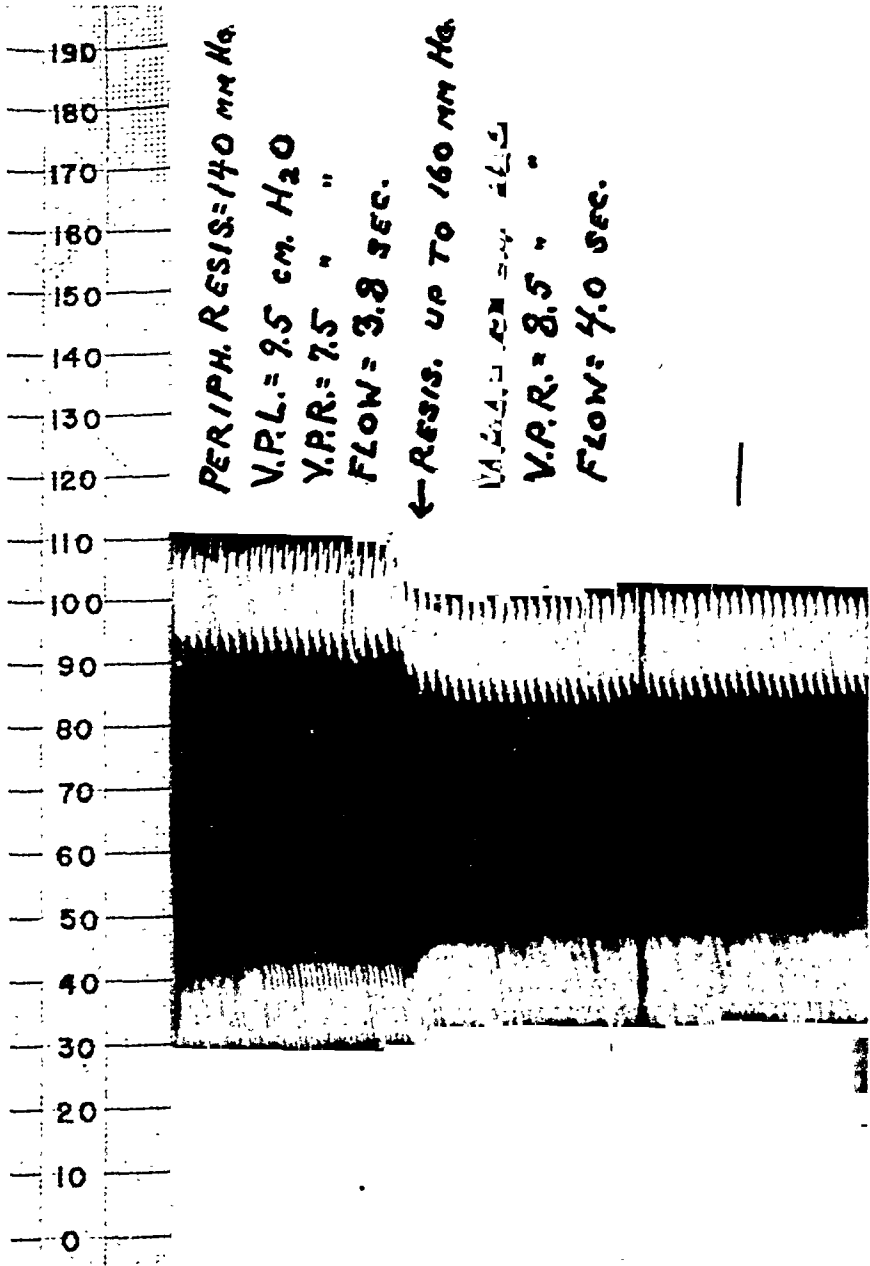


Fig. 4a.—Influence of blood pressure increase on the diastolic volume of the heart and the venous pressure. Peripheral resistance is the pressure under which the artificial resistance in the heart-lung apparatus was placed. VPL = venous pressure on the left in cm. of water. VPR = venous pressure on the right in cm. of water. Flow is number of seconds needed for 50 c.c. of blood to pass from the left ventricle into the aortic system, exclusive of the amount flowing into the coronary arteries.

the transverse diameter of this normal heart would be approximately 7 mm. if the increase in diastolic volume was 125 c.c. These data give us the order of magnitude of the increase that would take place in the diastolic volume and transverse diameter of a normal sized human heart if its work per beat were increased approximately four times by increasing the stroke output four times. We have repeated this type of experiment many times in the course of this investigation and the result has always been the same. Increasing the work of the heart by increasing its output always causes dilatation of the heart, and, at the same time, there is an increase in the venous pressure in both the left and right auricles.

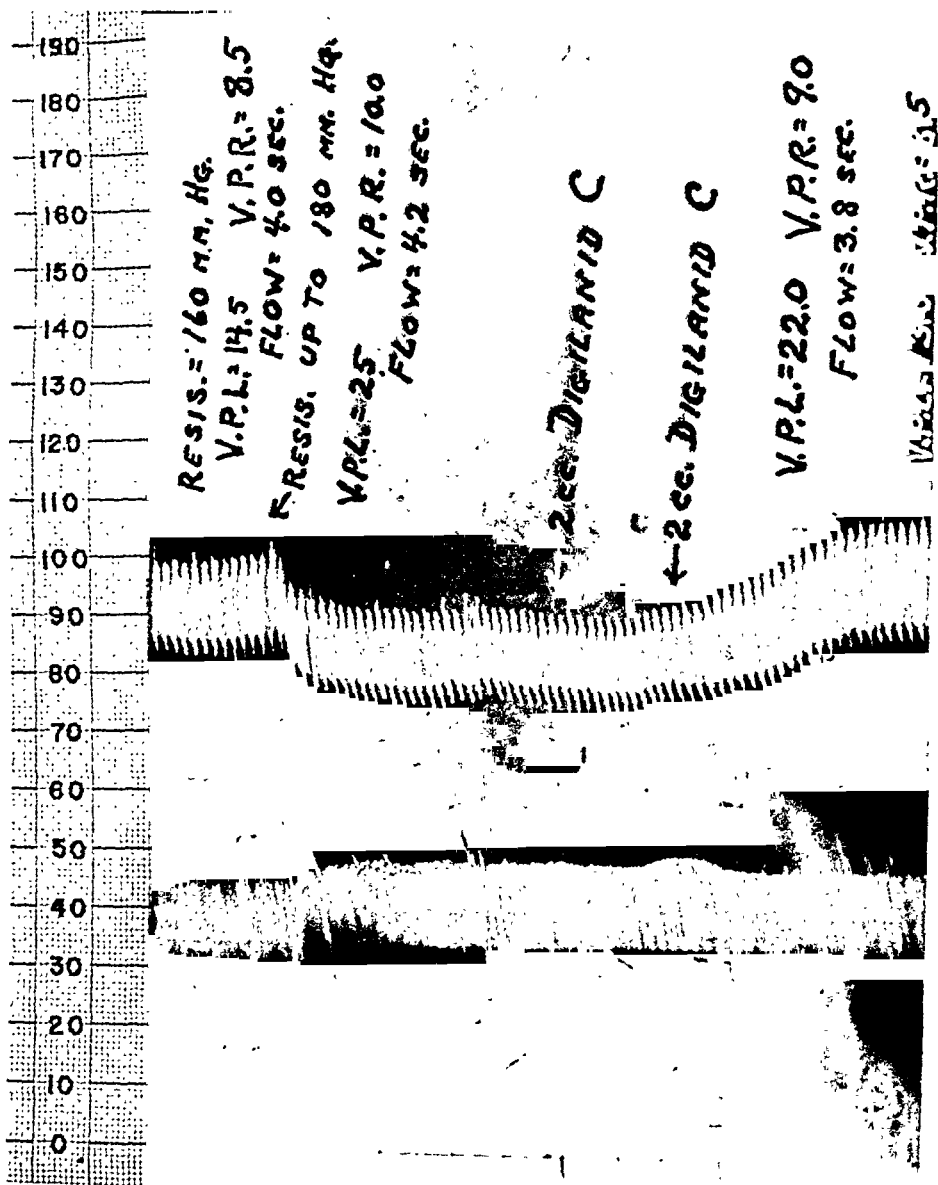


Fig. 4b.—Continuation of 4a. Another increase in peripheral resistance was brought about at the point marked by the arrow. Four c.c. of digilamid C were introduced at point marked on curve.

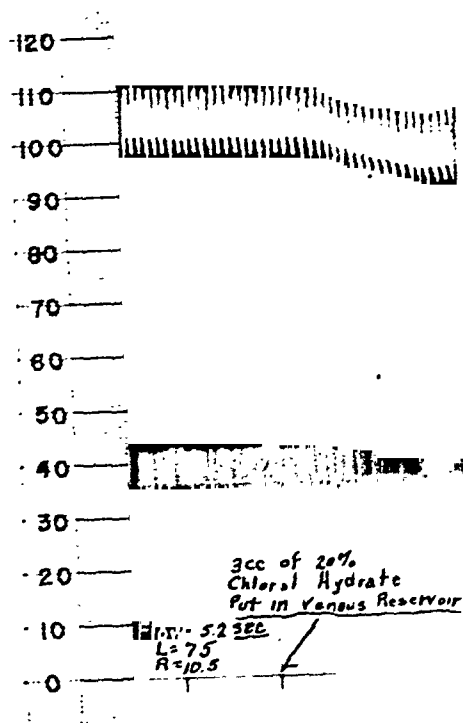


Fig. 5a.—Experiment with chloral hydrate. Upper curve, cardiometer tracing. Next curve below this, blood pressure record of Straub manometer. *L* is the venous pressure on the left. *R* is the venous pressure on the right.

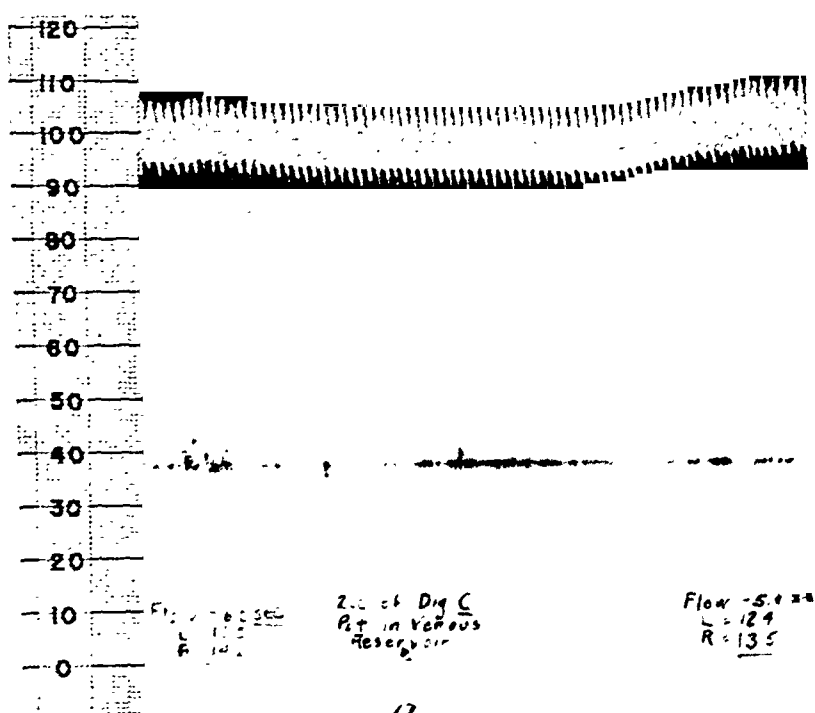


Fig. 5b.—Continuation of 5a. One and one-half cubic centimeters of 20 per cent chloral hydrate solution have again been added, and continuous dilatation takes place. At the point marked on the signal curve, 2 c.c. of digilanid C were put into the reservoir, effecting decrease in diastolic volume, increasing the rate of flow, and decreasing the venous pressure.

Fig. 4a shows the effect of increasing the artificial peripheral resistance from 140 to 160 mm. Hg. The blood pressure increased from 190/144 to 210/162 mm. Hg. The minute volume, as measured by the flow meter in the arterial system, dropped from 790 c.c. to 750 c.c., a difference which depends largely upon increased flow in the coronary system caused by the rise in mean arterial pressure. The stroke output, as measured by the difference between the systolic and diastolic volumes on the cardiometer record, showed no measurable change. The ventricles dilated 8 c.c., and the venous pressure went up from 9.5 c.c. to 15 cm. of water in the left auricle and from 5.5 cm. to 8.5 cm. of water in the right auricle. Fig. 4b shows the effect of further increasing the artificial resistance to 180. The blood pressure rose to 223/187, and the heart di-

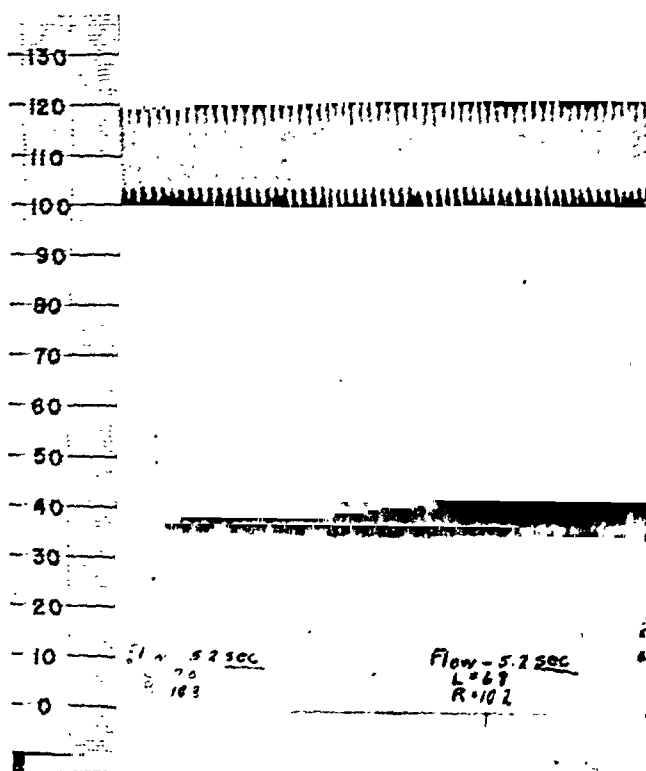


Fig. 5c.—Continuation of 5b. Continued effect of digitals, reducing the diastolic volume to normal and bringing back the velocity of flow in the aorta to the original level.

lated another 8 c.c. The venous pressure went up to 25 cm. on the left and 10 on the right. The minute output, as measured by the stromuhr, fell to 715 c.c. per minute. The difference between 790 and 715 c.c. per minute was largely the result of the increase in flow in the coronary system caused by the increased mean blood pressure. The difference between the systolic and diastolic volumes on the cardiometer tracing showed no measurable change in stroke output. Rises in blood pressure in a good heart-lung preparation are not accompanied by a fall in cardiac output.

Four c.c. of digilanid C were then introduced into the reservoir, and, within a short period of time, with the blood pressure remaining at 227/179, the venous pressure started to fall and the output to increase. At the end of the curve the venous pressure had declined on the left to 13, and, on the right, to 8.5 cm. of water, and the minute volume had increased to 790 c.c. At the same time the diastolic volume had decreased 15 c.c. Two minutes later the venous pressure had come down to 8.8 cm. on the left and 7.5 cm. on the right, and the minute volume had increased to 835 c.c. This digitalis effect indicates that considerable spontaneous heart failure was present, despite which the Starling "law of the heart" held good.

Figs. 5a, b, and c illustrate well an experiment in which chloral hydrate was used to produce failure of the dog's heart. Before the chloral hydrate was given, the venous pressure on the left was 7.5, and, on the right, was 10.5. The minute volume of flow through the flow meter was 575 c.c. per minute. The blood pressure was 125/92. At the point marked by the arrow, 3 c.c. of a 20 per cent solution of chloral hydrate were put into the venous reservoir; the latter contained approximately 1000 c.c. of blood. Within a minute after introducing the chloral hydrate the heart had dilated 7 c.c. and the venous pressure had risen to 10.3 on the left and 12.3 on the right. At the same time the cardiac output, as measured by the stromuhr, had fallen to 540 c.c. per minute, and the blood pressure was 122/92. A little later, 1.5 c.c. of a 20 per cent solution of chloral hydrate were introduced into the reservoir, and the venous pressure on the left rose to 13.5 and on the right to 14.2. At the same time the diastolic volume of the heart increased 2 c.c. more, the flow decreased to 500 c.c. per minute, and the blood pressure was 115/90. This is illustrated in the first part of Fig. 5b. If we had increased the input into the right auricle so as to bring the work of the heart back to its original value, the dilatation would have increased even more and the venous pressure would have risen higher. As it was, the heart was performing less work at a greater diastolic volume and with an increased venous pressure. At the point marked with a small arrow, 2 c.c. (0.4 mg.) of digilanid C were put into the venous reservoir, and, within one minute, the heart had decreased 4 c.c. in diastolic volume, as illustrated on the curve, and the venous pressure had dropped to 12.4 on the left and 13.5 on the right. At the same time the minute volume in the stromuhr had gone up to 520 c.c. Two c.c. more of digilanid C were now put into the venous reservoir, and, approximately 15 minutes after the first digilanid had been introduced, the diastolic volume of the heart was 5 c.c. smaller than at the beginning of the experiment, as shown in Fig. 5c. The venous pressure on the left was back to the normal of 6.8, and, on the right, to 10.2. The minute volume was, as originally, 575, and the blood pressure was 125/93. This experiment, making use of chloral hydrate to produce a hypodynamic heart muscle, was repeated a number of times on a number of dogs' hearts and the results were al-

ways the same. Chloral hydrate produced dilatation of the heart and an increase in venous pressure. There was some tendency to decreased stroke output, so that the work of the heart decreased. Digitalis tended to bring back the venous pressure to the normal, to decrease the diastolic volume to normal, and to increase the output to the original amount per beat.

A close examination of the cardiometer record during heart failure shows how the changes associated with heart failure are brought about. As the heart failure starts to manifest itself, we note that there is a slight increase in the systolic volume of the heart, indicating that the heart is emptying itself a little less each beat, or, in other words, that the stroke output has slightly decreased. The stroke output continues to decrease, but sooner or later seems to become stationary. In the meantime, the diastolic volume has increased because a greater amount of blood is retained in the ventricle at the end of systole and nearly the same amount comes in from the venous reservoir during the succeeding diastolic period. Therefore, the total diastolic volume increases somewhat. Decrease in the systolic output and increase in the diastolic volume may continue until the heart stops beating, but, as a rule, a point is reached at which the diastolic volume does not increase or increases only very slowly. The systolic volume may now decrease somewhat; in other words, the systolic output may increase until the original level is reached or nearly reached. In severer degrees of poisoning the original stroke output is never reached despite the diastolic volume increase. In the meantime, the venous pressure has increased on both the left and the right side of the heart. A more or less steady state is now achieved, in which, with an increased diastolic volume and an increased venous pressure, the stroke output has increased either to the original value or possibly is a little below it. The mechanism of the increase in diastolic volume is to be found in the decreased systolic output once the poison has produced a hypodynamic state of the heart muscle. The retained blood, plus the blood flowing in from the venous reservoir, tends to increase the diastolic volume. At the same time the venous pressure rises because there is some slowing up of the flow from the venous reservoir into the heart. If the venous pressure did not rise somewhat, the diastolic volume could not increase. In order to get an increase in diastolic volume it is necessary to increase the initial (diastolic) tension on the cardiac muscle fibers.

One of our many experiments with chloral hydrate as a cardiac poison has some additional points of interest to the clinician, in that both asystole and auricular fibrillation were produced, and the administration of a digitalis glycoside, digilanid C, apparently resulted in restoration of normal rhythm. This heart had been experimented upon for about one-half hour before starting the chloral hydrate. At the start of the experiment with chloral hydrate, the blood pressure was 147/127, the cardiac

output was 580 c.c., neglecting the coronary flow, and the venous pressure on the left was 8.2 and on the right 6 cm. Two portions of 2 c.c. each of a 10 per cent solution of chloral hydrate were introduced into the venous reservoir; this caused an increase of about 20 c.c. in the diastolic volume of the heart and a fall in the minute output, as measured by the stromuhr, to 500 c.c. per minute, and the blood pressure fell to 136/116. Four c.c. of a 10 per cent solution of chloral hydrate were then added to the venous reservoir, and within one and one-half minutes the heart

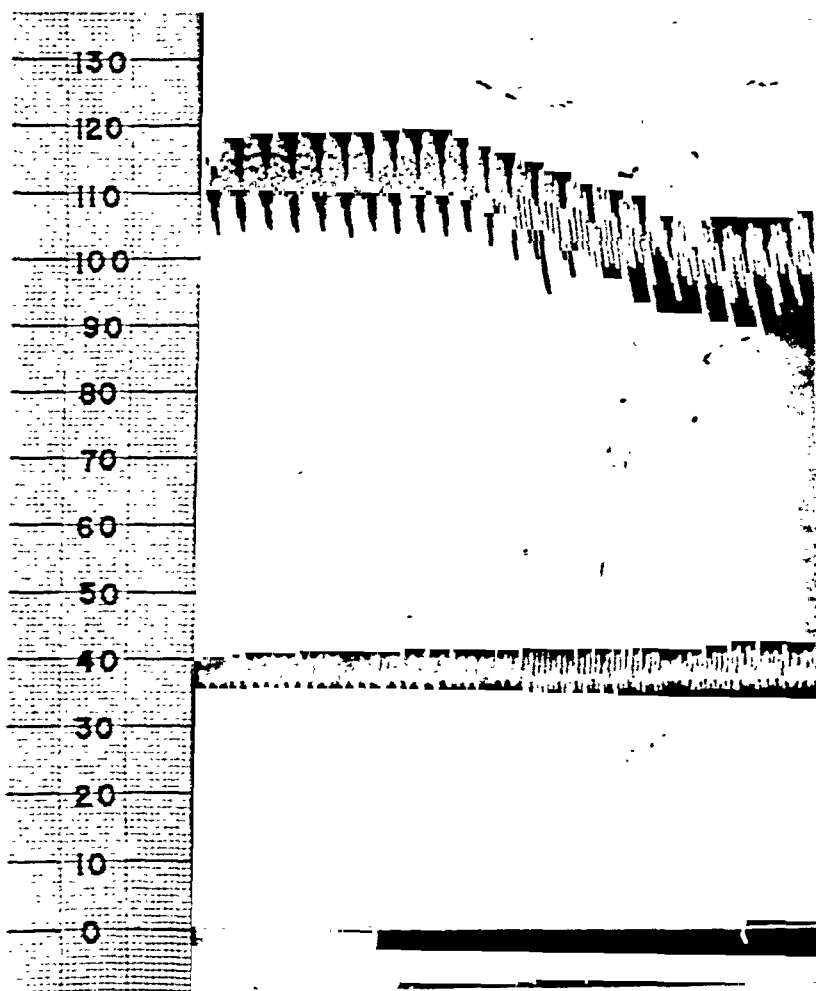


Fig. 6a.—Effect of diphtheria toxin on the heart size. At the point marked 6 on the signal magnet, diphtheria toxin was introduced. At the point marked 7 on the signal magnet, velocity of blood flow in the aorta and venous pressure and diastolic volume increase were measured.

started to dilate greatly, the rate of the heart to slow appreciably, and the venous pressures to rise markedly. In a very short time the heart stopped beating, at which time the diastolic volume had increased 65 c.c. more and the venous pressures both on the left and right were 42 cm. of water: this was the height of the venous reservoir above the right auricle. The heart stopped beating for only a few seconds, and then occasional beats appeared. As the heart started to beat again the dilatation receded until there was a total increase of 40 c.c. in diastolic volume

above that before any chloral hydrate had been given. The venous pressure was 20 on the left and 10 on the right. When auricular fibrillation set in, the heart dilated about 44 c.c. again. The venous pressure then rose to 40 on the left and 36 on the right, and the minute output was so slight that it was impossible to measure it accurately. At the point of greatest dilatation, 4 c.c. (0.8 mg.) of digilanid C were given. After four minutes the heart became regular and the dilatation receded until the diastolic volume of the ventricles was back to its original value. The venous pressure finally became 10 on the left and 6 on the right. Analysis

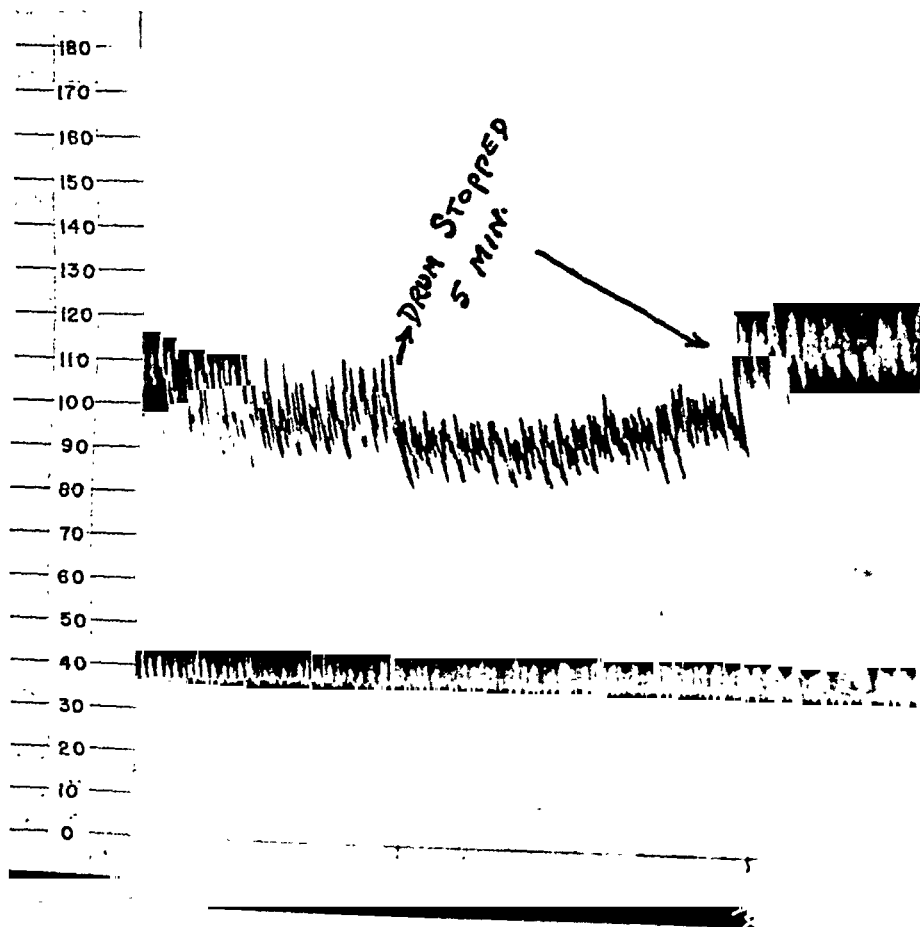


Fig. 6b.—Continuation of 6a. Continued dilatation of the heart under the influence of diphtheria toxin; marked irregularity. At the point marked 13 on the signal magnet, digilanid C was introduced, with consequent decrease in the diastolic volume of the heart.

of these results shows again that the effect of chloral hydrate as a cardiac poison is to cause a rise in venous pressure, dilatation of heart, and decrease in cardiac output. Chloral hydrate may result in asystole, from which the heart may recover. Auricular fibrillation may then develop, with an increased dilatation of the heart and an increase in venous pressure. Digilanid C may stop the auricular fibrillation, after which the diastolic volume may come back nearly to normal, the venous pressures

may be restored approximately to normal, and the cardiac output may become the same as before chloral hydrate was given.

We carried out three experiments in which diphtheria toxin was used to poison the heart. Two of these experiments were done with the heart-lung preparation without the oxygen consumption attachment, and one was carried out with the oxygen consumption apparatus. It is necessary to use very strong diphtheria toxin in order to produce heart failure within the short period of time necessary for these experiments. These strong solutions of diphtheria toxin tend to produce disturbances such as heart block, extrasystoles, auricular fibrillation, and pulsus alternans. These abnormalities make it very difficult to compute the work of the heart accurately because of the irregularity in the blood pressure.

Fig. 6a shows the cardiometer and blood pressure record in an experiment with diphtheria toxin ($L+ = .0092$) obtained from the Eli Lilly Company by Dr. Larson of the Department of Bacteriology at the University of Minnesota. At the start of the experiment the minute output was 790 c.c., neglecting the coronary flow, and the venous pressure on the left was 10.2, and, on the right, 10.3 cm. of water. The blood pressure was 127/109. Twenty-four c.c. of the diphtheria toxin were injected into the reservoir, which contained approximately 1000 c.c. of blood. As this seemed to have only a slight effect on the venous pressure and the size of the heart, within $1\frac{3}{4}$ minutes we added another 16 c.c. Within 45 seconds after this second dose of diphtheria toxin, the venous pressure on the left side had risen to 32.5 cm. and on the right to 13.5 cm., and the heart volume, as shown in Fig. 6a, increased 16 c.c. The mean blood pressure could not be accurately measured because of the irregularity of the heart, but the curve shows that it was somewhat less than before, whereas the minute volume (790 c.c.) had not decreased. A little later the heart became even more irregular, as is shown in the continuation of this curve in Fig. 6b. At the same time the heart continued to dilate until it was 30 c.c. larger than before the diphtheria toxin was given. At the point, marked 13 on the signal magnet curve in Fig. 6b, 4 c.c. of digilanid C were given. The venous pressures started to decline soon after the digilanid was given, and slowly decreased to 10.3 cm. on the left and 9.7 on the right in approximately 35 minutes. At this time the diastolic volume had decreased 28 c.c. In the meantime, the heart became regular, the output of the left ventricle, neglecting the coronary flow, remained at 790 c.c. per minute, and the blood pressure was 127/104.

In the other experiment with diphtheria toxin, we employed a weaker toxin ($L = 0.035$). At the start the venous pressure was 7.8 on the left and 11.2 cm. on the right; the flow was 600 c.c. per minute, measured in the flow meter; and the blood pressure was 122/110 mm. Hg. Two hundred twenty c.c. of diphtheria toxin were now introduced into the 1000 c.c. of blood in the reservoir. The heart started to dilate, the venous pressures went up to 11.2 on the left and 15.5 cm. of water on the right.

and the flow decreased to 500 c.c. At the same time the heart became very irregular. The heart had dilated about 15 c.c. at this time, and the flow, as measured in the flow meter, had fallen to 500 c.c. The inflow cock was now opened in order to obtain the same flow as at the beginning, and, with the minute flow at 600 c.c., the venous pressure rose to 20 cm. on the left and 21 cm. on the right. There was at this time a total dilatation of about 42 c.c. The mean blood pressure was very difficult to measure accurately because of the irregularity. We calculated that the mean value was approximately 119 mm. Hg. Therefore the left ventricle was doing about the same amount of work as at the beginning of the experiment, and the mean blood pressure determining coronary flow was, also, the same as at the beginning. Four c.c. of digilanid C were introduced into the reservoir, but the heart continued to be irregular, the venous pressures went up even higher than they had been, and the output decreased. The heart continued to dilate. It was evident that digilanid C would not restore the original condition of this heart muscle, and the experiment was soon discontinued. The experiments with diphtheria toxin show very definitely that this poison tends to produce a hypodynamic heart muscle, but the experiment is frequently complicated by cardiac irregularities. The venous pressure always rises at the same time that the ventricles dilate. There is a tendency toward a fall in the cardiac output which can be made good by increasing the inflow. Under these circumstances the heart dilates more and the venous pressures rise even more. If digilanid C is given soon enough, or if the degree of poisoning is not too great, normal conditions will be restored.

We performed a very large number of experiments in which chloroform was used to injure the heart. The chloroform was introduced into the air that was pumped into the lungs of the preparation, but it was found that it was very difficult to gauge the amount of chloroform accurately by this method, and, in many cases, although we were able to produce a hypodynamic heart muscle, it was very frequently impossible to make the conditions reversible with digilanid C because the poisoning had gone too far. The ventricles would begin to fibrillate, and the heart would stop beating.

Fig. 7a shows continued dilatation* of a dog's heart after chloroform was started. The signal marker shows a slight rise at the moment at which the chloroform was introduced. Shortly after this the heart dilated fairly rapidly. At the end of this curve the heart had increased 18 c.c. in diastolic volume after introducing the chloroform. The cardiac output remained the same as previously, namely, 1165 c.c. per minute. The blood pressure, which was this time taken with a mercury manometer, remained constantly at 84 mm. Hg. The venous pressure, which had been 7.5 cm. on the left and 7 cm. on the right, had gone up to 17 cm.

*In the chloroform series the position of the cardiometer curve is above the systolic; ergo, the position of the cardiometer curve is above the other experiments the position of the cardiometer tracing rises. In all the

on the left and 13 cm. on the right at the end of this figure. The heart continued to dilate for a period of about two minutes more, at which time the total dilatation of the heart was 35 c.c. and the flow meter measured a flow of 1040 c.c. per minute. The venous pressure had now gone up to 24 cm. on the left and 16.5 on the right; the blood pressure remained constantly at 84 mm. Hg. This is the condition as seen in Fig. 7b. At the end of this figure the signal marker shows where 4 c.c. of digilanid C were given, and Fig. 7c shows that the dilatation of the heart has receded. Calibration of this decrease in diastolic volume

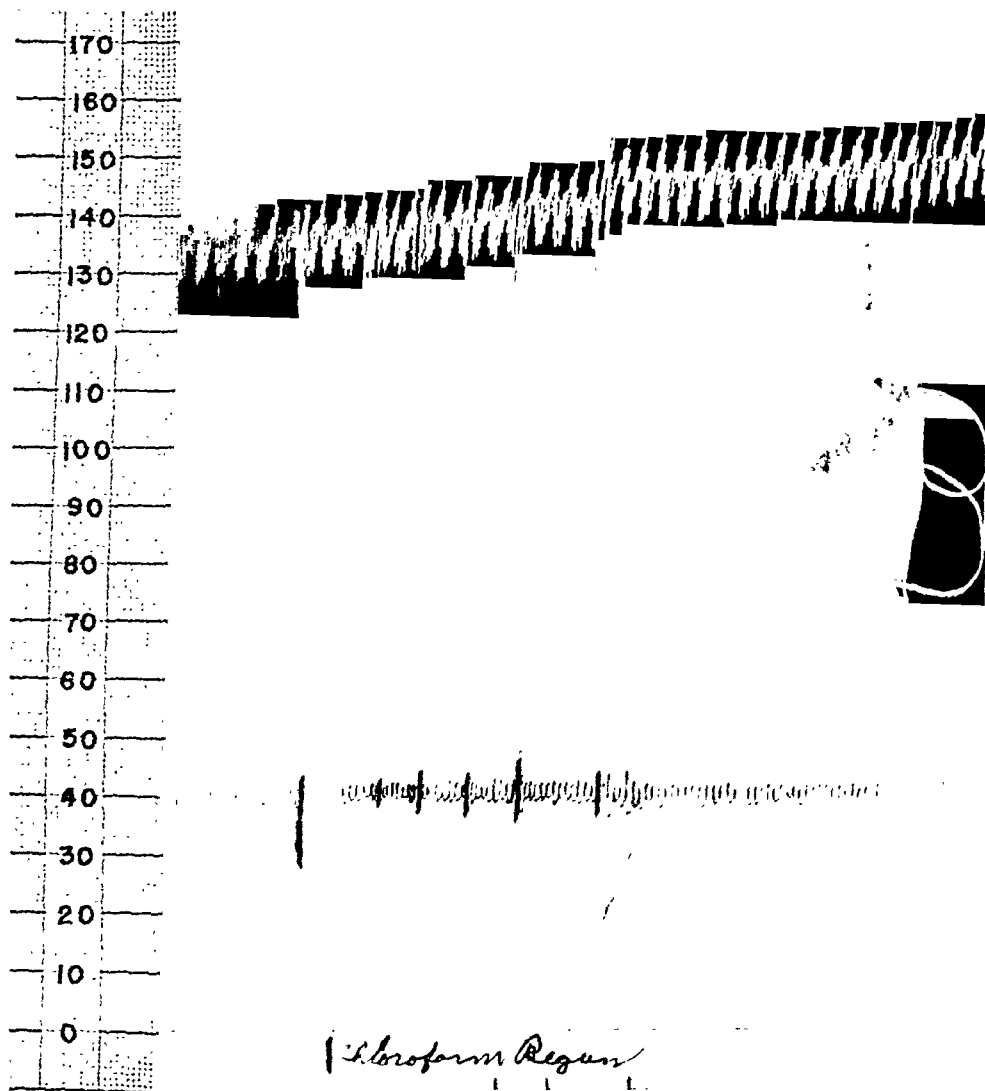


Fig. 7a.—Experiment with chloroform. Synchronous points on the cardiometer tracing, the blood pressure tracing, the signal magnet, and the time marker are shown by the three white marks. At the point on the signal magnet shown by the white mark below it, chloroform was introduced. In this curve the cardiometer lever is so placed that an upward deflection indicates diastole, and a downward deflection, systole. In other words, an upward deflection of the curve means dilatation. In this figure the blood pressure tracing is that of a mercury manometer. The zero point for this mercury manometer is the signal magnet line, which corresponds to the point zero on the scale to the left. Chloroform causes 18 c.c. enlargement of the diastolic volume at the end of this cardiometer tracing. The cardiac output remained constant. The per minute, exclusive of coronary flow. The blood pressure remained constant. The venous pressure was 7.5 on the left and 7 on the right at the beginning, and, at the end of this figure, had gone up to 17 on the left and 13 on the right.

showed that it amounted to 25 c.c., but the heart was still 10 c.c. larger than at the start of the experiment. The blood pressure remained the same. The minute volume, as measured in the flow meter, had now gone up to 1480 c.c. per minute, which represents a 24 per cent increase over the original output. The venous pressure went down to 13.5 on the left and 11.5 on the right. Undoubtedly, part of the increase in venous pressure and diastolic volume was the result of the fact that the work of the heart had been increased through increased minute volume by about 20-25 per cent. The many experiments with chloroform as the cardiac toxin showed that the heart invariably dilates, the venous pressures rise, and there is a tendency toward a decrease in the stroke output when the

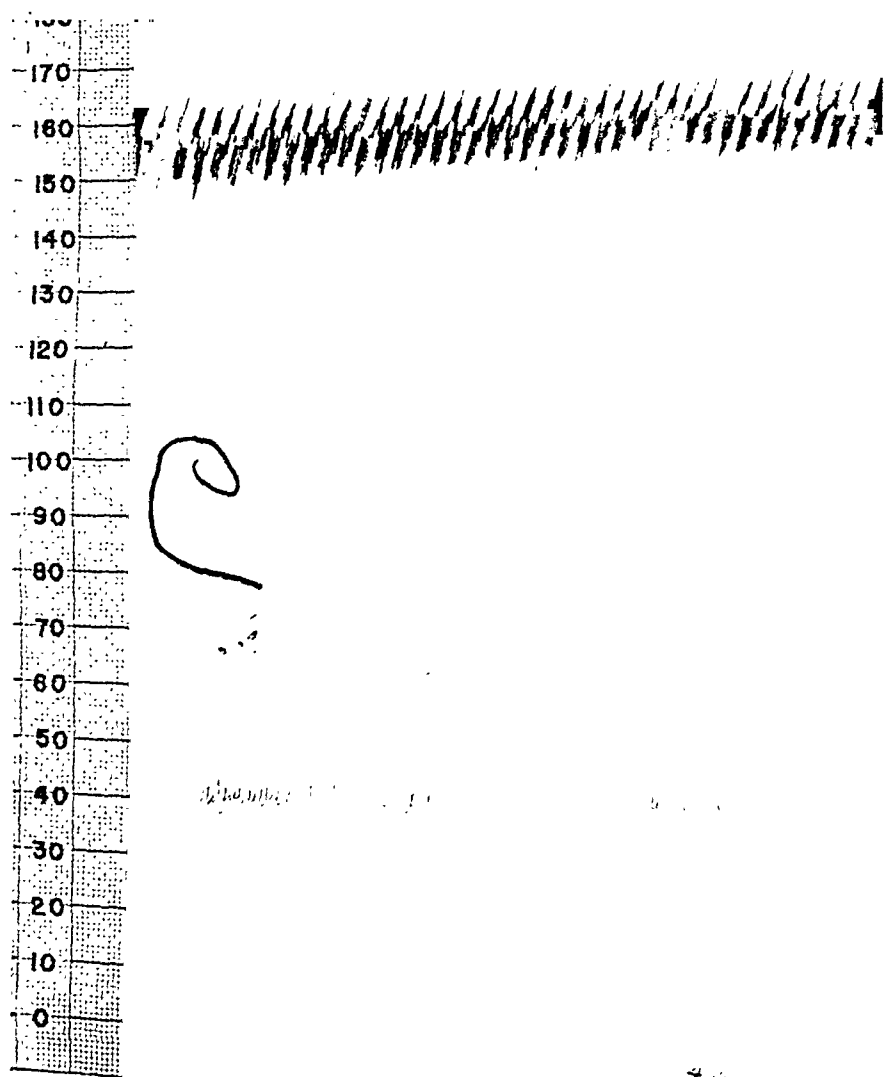


Fig. 7b.—This shows continued dilatation of the heart under the influence of chloroform. The total increase in the diastolic volume of this heart near the end of the curve at the point where the digilanid was introduced was 35 c.c., and the flow meter measured an output of 1040 c.c. per minute. Venous pressure on the left had gone up to 24 cm. and up to 16.5 on the right. At the point marked on the signal magnet, 4 c.c. of digilanid C were introduced.

poison begins to affect the heart muscle. If the heart muscle becomes only slightly hypodynamic the original stroke output may be restored. With greater degrees of poisoning the minute output would drop considerably. Frequently a digitalis glycoside (Cedilanid) will restore or nearly restore the original diastolic volume, the original venous pressures, and the original stroke output. If the poisoning has gone too far the glycoside may fail to restore the heart muscle to its original condition, the heart stops beating, and ventricular fibrillation usually ensues.



Fig. 7c.—Continuation of Fig. 7b. The dilatation of the heart slowly recedes, until, at the end of the curve, it has receded 25 c.c. At this time the flow meter measures an output of 1480 c.c. per minute. Venous pressure on the left is now down to 13.5, and, on the right, to 11.5.

The effect of alcohol upon the heart is essentially the same as that of chloroform, chloral hydrate, and diphtheria toxin. Fig. 8a shows an experiment in which 95 per cent alcohol was used. At the start of the experiment the volume flow was 600 c.c. per minute, the blood pressure, 129/97, and the venous pressure on the left 13.2, and on the right 9.6 cm. of water. At the point marked on the signal magnet, $2\frac{1}{2}$ c.c. of 95 per

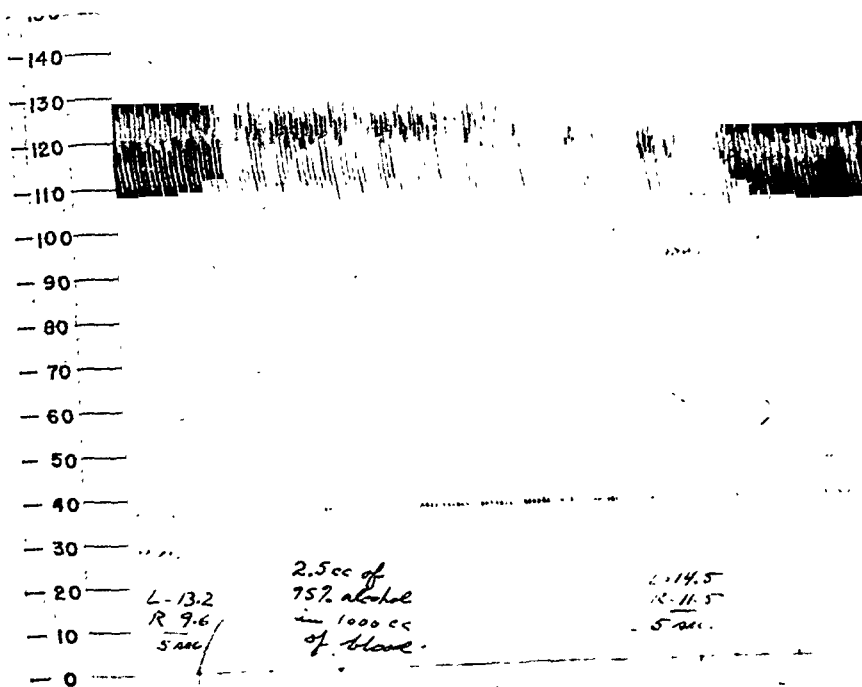


Fig. 8a.—This shows the effect of alcohol. At the point marked on the signal magnet, 2.5 c.c. of 95 per cent alcohol were introduced. Dilatation takes place, as seen at the end of the cardiometer tracing. In this case systole is up and diastole down. At the point marked on the signal magnet the flow is 50 c.c. in 5 seconds and the venous pressure on the left has gone up to 14.5 and on the right to 11.5.

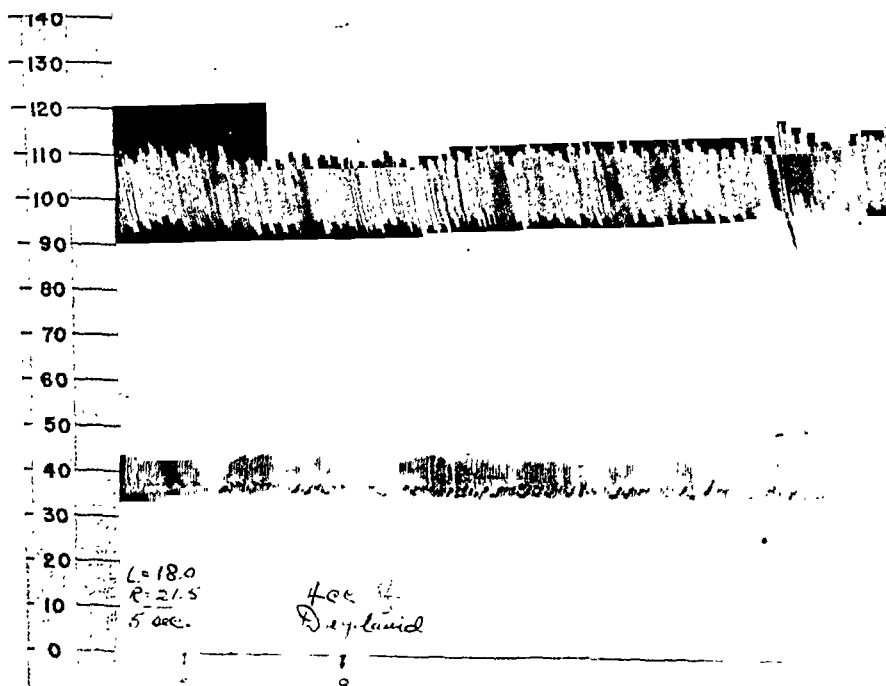


Fig. 8b.—Continuation of 8a. It shows continued dilatation. The venous pressure has gone up to 18 on the left and 21.5 on the right at the point marked 18 on the signal magnet; at this time the flow is still 50 c.c. in five seconds. Just before the point marked 18 on the signal magnet, the inflow was increased so that the minute flow went up to the original of 600 c.c. At the point "19," four c.c. of digilanid were given and there is some recession in diastolic volume. At the end of the figure this decrease in diastolic volume is about 5 c.c., and the venous pressure on the left is 16, and, on the right, 18.2, with a minute output of 650 c.c., excluding the coronary flow.

cent alcohol were added to the 1000 c.c. of blood in the reservoir. Within one and one-fourth minutes the venous pressure on the left had risen to 14.5, and, on the right, to 11.5, and the diastolic volume of the heart had decreased 7 c.c. The minute output remained unchanged and the blood pressure was 125/95, which was approximately the same as at the start of the experiment. Later, 2½ c.c. more of alcohol were given and the heart dilated again. The venous pressure rose to 16.2 on the left and 13 on the right, and the minute volume fell to 575 c.c. An additional 2½ c.c. of alcohol were given. The heart continued to dilate and the venous pressure to rise until there was a total dilatation of 16 c.c. and the venous pressure was 18.8 on the left and 18.8 on the right. At this time we increased the inflow into the heart because the output seemed to be decreasing considerably. This caused an increased dilatation. Somewhat later we tried the effect of giving digilanid C. At the point marked on the signal magnet, in Fig. 8b, 4 c.c. of digilanid C were added to the blood in the reservoir. At this time the venous pressure on the left was 18, and, on the right, 21.5; the minute output was 600 c.c.; and the blood pressure was 125/97. Three minutes after giving digilanid C the diastolic volume had decreased 5 c.c., as shown near the end of Fig. 8b. Six minutes later the diastolic volume had receded a little more, so that the total decrease in diastolic volume was 7 c.c. and the venous pressure on the left was 16 and on the right 18.2. The minute output had risen to 650 c.c. The blood pressure was approximately 130/96. In this experiment the increased diastolic volume of the ventricles only decreased about 35 per cent under the influence of the digilanid C, partly because we gave too much alcohol or waited too long before giving the glycoside, and partly also because the work of the heart had increased about 10 per cent. This experiment illustrates that when alcohol was used as a poison for the heart muscle, the blood pressure varied very little throughout the experiment, the venous pressure rose very definitely on both sides of the heart, and the heart dilated moderately. At the same time, when the heart failure became severe there was some diminution in the minute output of the heart. A digitalis glycoside (digilanid) tended to decrease the venous pressure and the diastolic volume of the heart and to increase the minute flow.

Only one experiment was performed on the heart-lung preparation without the oxygen consumption apparatus in which potassium chloride was used as the heart poison. Potassium chloride tends to produce heart block and extrasystoles, and these complicate experiments. In this one experiment we made use of a dog weighing 25 pounds. The artificial resistance was set at 100 mm. Hg. The inflow was adjusted so that there was a flow of 600 c.c. per minute in the flow meter. The venous pressure was 7.6 on the left and 6.6 on the right. The minute flow, the venous pressures, and the diastolic volume remained constant throughout the preliminary period of four minutes, during which the blood pressure was

127/102. One c.c. of a 10 per cent solution of potassium chloride was added to the 1000 c.c. of blood in the reservoir, and, within two minutes, the venous pressure on the left had risen to 8.5 and on the right to 7.5. The output remained at 600 c.c. a minute. Then another c.c. of the potassium chloride solution was added, and, two and one-half minutes later, the venous pressure on the left was 9.5, and, on the right, 8, with 600 c.c. per minute passing through the flow meter. Three c.c. more of the 10 per cent potassium chloride solution were added, and, four minutes later, the venous pressure on the left had risen to 19 and on the right to 13.2. At this time the cardiac output, minus the flow in the coronary vessels, was 555 c.c. per minute and the heart rate had slowed down very materially. The diastolic volume had increased 10 c.c. The heart became much slower and then very irregular because of numerous extrasystoles. At this time, 5 c.c. of digilanid C were given, but the preparation continued to fail, and, 17 minutes after giving the first portion of digilanid C, the venous pressure on the left was 21, and, on the right, 16; the diastolic volume of the heart had increased 30 c.c. beyond its original volume and the cardiac output, as measured in our flow meter, had fallen to 410 c.c. per minute. At this time the rate of the heart was about 45, whereas it had been 118 before any potassium chloride had been given. The heartbeat was very irregular, and, although the diastolic blood pressure remained fairly constant at 97, the systolic blood pressure varied enormously because of the irregularity of the heart. During the period of greatest dilatation and slowing of the heart, the venous pressures finally rose to approximately 35 cm. both on the left and right. Another c.c. of digilanid was introduced into the reservoir, and, 18 minutes later, the heart had recovered somewhat. The rhythm became perfectly regular, but the rate was 72. The venous pressure fell to 16.5 on the left and 13.5 on the right. The cardiac output rose to 535 c.c. per minute. The blood pressure at this time was 137/97, and the diastolic volume receded until it was only 8 c.c. larger than at the start of the experiment. From this time on there was very little change in the cardiac output, the venous pressures, or the diastolic volume. For a period of 32 minutes after making these measurements they remained constant at the above values. At this time we stopped the experiment because it was apparent that there was not going to be any more improvement in the heart. The effects of the potassium chloride were to cause dilatation of the heart, increase in the venous pressures, decrease in the cardiac output, and slowing and irregularity of the heartbeat. Digilanid seemed to cause disappearance of the irregularity of the heart and a decrease in the cardiac volume and in the venous pressures, but it did not restore them completely to the values present before the potassium chloride had been given. Digilanid also produced an increase in the cardiac output, but here also it did not completely restore it to what it was before the potassium chloride had been given.

OXYGEN CONSUMPTION EXPERIMENTS

The above-mentioned experiments would make it seem extremely probable that the oxygen consumption of the mammalian heart increases at the same time that the mechanical work of the heart either remains the same or decreases when the heart muscle is made hypodynamic by poisoning. We therefore proceeded to make use of the Visser oxygen consumption apparatus in order to ascertain simultaneously external cardiac work and oxygen consumption, or total energy release of the heart.

We calculated the work of the left ventricle by multiplying the minute flow in the arterial system by the mean blood pressure. This flow is measured by a Stolnykow stromuhr, inserted in the arterial line. We did not measure the blood flow in the coronary arterial system, so that the work of the left ventricle as thus calculated was probably often 20 to even 30 per cent less than the actual work because of this neglect of the coronary flow. We also assumed that the work of the right side of the heart was one-third that of the left. This is the usual assumption in this type of experimental procedure, especially in view of the increased pulmonary artery resistance caused by the pressure of the cardiometer membrane upon the pulmonary artery. We have neglected the kinetic energy of the mass of blood ejected from the heart, but this is a common procedure in elementary physiology because it is usually assumed that the kinetic energy factor is not more than 5 per cent of the total work of the ventricles. Another thing to be kept in mind is that, although we attempt to measure the work of the ventricles, the work of the auricles is neglected. There is no question that the auricles perform a not inconsiderable amount of work, especially when a cardiometer is placed tightly around the ventricles. Therefore, the work of the heart as we calculated it is undoubtedly considerably less than the actual work, so that our calculated mechanical efficiency is not as high as it would be if it were ascertained by a more accurate method of measurement. At the same time, changes in mechanical efficiency are accurately ascertained by this method. Our mechanical efficiencies are of the same order of magnitude as those observed by Peters and Visser⁵ and Katz and Mendlowitz.⁶

Our first experiment with the oxygen consumption apparatus was carried out with chloral hydrate as the poisoning agent. The dog weighed 19 pounds. The temperature of the water bath in which the heart lung apparatus was immersed was kept at 35° C. The blood pressure was 165/120, giving a mean of 14.2 cm. of mercury. The volume flow was 470 c.c. per minute. The external work of the left ventricle is calculated from these figures as 89×10^6 ergs. The external work of the right ventricle, calculated as one-third of this, is 29.7×10^6 ergs. The total work of the ventricles is therefore 118.7×10^6 ergs. Using the mechanical equivalent of heat, this amount of work is equal to 2.8 calories. The oxygen consumption of the heart-lung preparation was measured over a period of three minutes, and one-third of this was taken

as the number of calories of oxygen consumption per minute. This oxygen consumption was found to be 85 calories per minute. The oxygen consumption of the lung itself is calculated at one-fifth of this, or 17 calories, leaving an oxygen consumption for the heart of 68 calories. The mechanical efficiency, as calculated from these figures of 68 calories oxygen consumption for the heart and 2.8 calories of external ventricular work, was 4.1 per cent.

Now 6 c.c. of a 20 per cent solution of chloral hydrate were put into the reservoir containing the blood. Eleven minutes after the chloral hydrate had been given, the following observations were made. The blood pressure was 168/113, giving a mean of 14 cm. of mercury. The minute output, as measured by the flow meter, was 455 c.c. per minute. The external work of the ventricles was equivalent to 2.7 calories. The oxygen consumption of the heart-lung preparation for one minute was 131 calories, and, of the lung, 17 calories, leaving 114 calories as the oxygen consumption of the heart per minute. The mechanical efficiency under these circumstances was calculated as 2.4 per cent, which was a fall of 41 per cent within eleven minutes after giving the chloral hydrate. The dilatation of the heart at this time, as measured by the cardiometer, was 21 c.c.

Six minutes after 4 c.c. (0.8 mg.) of digilanid were given, the blood pressure was 167/115, giving a mean blood pressure of 14.1 cm. of mercury. The minute output of the heart at this time, as measured by the flow meter, was 526 c.c. The external work of the ventricles for one minute, as calculated in calories from the mean blood pressure and the flow, was 3.2 calories. The oxygen consumption of the whole preparation for one minute was 118 calories. Subtracting 17 calories for the oxygen consumption of the lung for one minute leaves 101 calories for one minute. This gives a mechanical efficiency of 3.2 per cent six minutes after digilanid was given, or an increase in mechanical efficiency of 33 per cent. The diastolic volume now showed approximately no enlargement. Nine minutes after giving the digilanid C the external work of the two ventricles, as measured in calories, was 2.9 calories, and the oxygen consumption of the heart for one minute was 88 calories. This gives a mechanical efficiency of 3.3 per cent, or a 37 per cent increase within nine minutes after digilanid C had been given.

We tested the cardiometer very carefully in this experiment, and found that there were no leaks. This was a good preparation from the start. A check made at the beginning of the experiment showed that for eight minutes of the normal period there was no dilatation of the heart, but rather a 1 c.c. reduction of the diastolic volume. At the same time we measured a reduction in the external work of the left ventricle of about 1 per cent. This shows that this was an exceptionally good experiment, and that spontaneous failure proceeded very slowly. The dilatation and the change in oxygen consumption and mechanical

efficiency after the chloral hydrate was given may therefore be well attributed to the effect of chloral hydrate alone. In the same way it may be said that the effect of the digilanid alone caused the dilatation to recede and the mechanical efficiency to increase after it had been reduced by the chloral hydrate. This experiment proves that chloral hydrate causes a reduction in the mechanical efficiency of the heart muscle at the same time that it produces an increase in the diastolic volume of the heart.

A second experiment was done with chloral hydrate as the poisoning agent, making use of the Visscher oxygen consumption apparatus to ascertain mechanical efficiency. In this experiment it took us a long time to get the preparation made. Therefore, the heart had dilated considerably before it was put into the cardiometer. In this experiment the calculated external work of both ventricles for one minute was 65.2×10^6 ergs, which is equal to 1.6 calories when the mechanical equivalent of heat is used for the transformation of ergs into calories. The oxygen consumption of the heart for one minute was 172.5 calories, and the mechanical efficiency was therefore 0.92 per cent.

Now $4\frac{1}{2}$ c.c. of a 20 per cent solution of chloral hydrate were put into the venous reservoir. Within a short period of time there was a distinct dilatation of the heart, amounting to about 10 c.c., but, as there was a slight leak in the cardiometer, the dilatation was probably greater than this. The minute output decreased to 142 c.c. per minute, as measured in the flow meter. It was impossible to increase this minute output because the stopcock between the venous reservoir and the right auricle was wide open. The external work of both ventricles per minute was now 0.78 calories. The oxygen consumption of the heart alone for one minute was 191.9 calories. This gave a mechanical efficiency of 0.46 per cent. The mechanical efficiency fell from 0.92 per cent to 0.46 per cent after the use of chloral hydrate, that is, to one-half what it had been previously.

Four c.c. of digilanid C were now put into the reservoir, and the cardiometer tracing showed a distinct reduction in size five minutes afterwards. The external work of both ventricles was calculated as 2.6 calories of ventricular work. The oxygen consumption of the heart was 133.9 calories. This gives a mechanical efficiency of 1.9 per cent after the digitalis glycoside had been given. This experiment shows very definitely that, when the heart muscle was poisoned with chloral hydrate, the mechanical efficiency diminished to one-half its previous value, and the use of digilanid resulted in an increase in the mechanical efficiency of 300 per cent. In this experiment there was a large spontaneous loss of mechanical efficiency before the poison was administered, part of which loss was removed by the use of the digitalis glycoside.

One more experiment was performed with chloral hydrate. This was again a poor preparation because of the long time consumed in making it, in fitting the cardiometer, and getting everything to work accurately.

After the heart-lung preparation had been completed, we had trouble with the apparatus, the valves, and the tubing, so that one and one-half hours elapsed between the time of completing the heart-lung preparation and the time at which it was finally put into the cardiometer. During this period the heart had dilated very greatly, so that it completely filled the cardiometer and therefore could not dilate. The temperature of the water bath was 34° C. Before the chloral hydrate was given, the output of the left ventricle, as measured in the flow meter, was 300 c.c. per minute. The blood pressure was 165/105. The external work of the two ventricles was calculated from these data as 1.6 calories per minute. The oxygen consumption of the heart alone was 384 calories, giving a mechanical efficiency of 0.4 per cent. Now 3 c.c. of a 20 per cent solution of chloral hydrate were introduced into the venous reservoir, but there was no dilatation, which corresponds with the fact that dilatation was almost impossible because the ventricles practically filled the cardiometer. On the other hand, there was a distinct fall in the blood pressure, and the stroke output seemed to be definitely less. An attempt was made to increase the inflow, but this was not successful because the heart could not dilate. After the heart had been under the influence of the chloral hydrate for four minutes, the minute output of the left ventricle had decreased to 90.5 c.c. per minute and the blood pressure was 125/85. The external work of both ventricles was 17×10^6 ergs, which is equivalent to 0.4 calories. The oxygen consumption of the heart alone for one minute was 374 calories, which gives a mechanical efficiency of 0.1 per cent. Now 4 c.c. of digilanid C were introduced into the reservoir, and, within 10 minutes, the minute volume, as measured in the flow meter, rose to 176 c.c. and the blood pressure was 155/90. The external work of the two ventricles was now equivalent to 0.9 calories. The oxygen consumption of the heart was 364 calories, which gives a mechanical efficiency of 0.25 per cent. It will be noted that this experiment was done at practically constant diastolic volume because the heart filled the cardiometer. In accordance with this, the oxygen consumption remained practically constant throughout the experiment. On the other hand, the external work of the heart decreased greatly. This experiment shows that, under the influence of chloral hydrate, even when the ventricular volume remained constant, there was a decrease in the mechanical efficiency, and the effect of digilanid C was to increase the mechanical efficiency.

Our next experiment on oxygen consumption was performed with alcohol as the heart poison. The heart, taken from a 24-pound dog, seemed to be in excellent condition. Some dilatation took place before the cardiometer was placed over the ventricles, but, after the preparation was started, the heart did not dilate over a period of six minutes. The minute volume also remained constant, as ascertained by four different measurements within a period of four minutes. This minute volume was

405 c.c. per minute. The blood pressure was 205/120, giving a mean of 162. The external work of the two ventricles was 2.8 calories. The heart consumed 225 calories of oxygen per minute, giving a mechanical efficiency of 1.2 per cent. A couple of minutes later a second measurement of the external work of the two ventricles showed that it was 2.7 calories. The oxygen consumption of the heart itself was 249 calories per minute giving a mechanical efficiency of 1.1 per cent. Now 6 c.c. of alcohol were introduced into the venous reservoir. Eleven minutes after the alcohol had been given, the heart had dilated about 6 c.c. and the minute output of the left ventricle had declined slightly (to 395 c.c.). The blood pressure had fallen to 200/115, giving a mean blood pressure of 158. The external work of the two ventricles was 2.6 calories. The oxygen consumption of the heart alone was 268 calories per minute, giving a mechanical efficiency of 0.95 per cent.

Two c.c. more of alcohol were added, and, 13 minutes later, the diastolic volume increased a little more. The minute output had now fallen to 306 c.c., and the blood pressure was 195/115, giving a mean blood pressure of 155. The external work of the two ventricles was 2.0 calories. The oxygen consumption of the heart during this period was 278 calories per minute, giving a mechanical efficiency of 0.7. Therefore, 30 minutes after the first alcohol had been introduced into the system the mechanical efficiency had fallen 36 per cent. There were now 8 c.c. of alcohol in the system, giving approximately an 0.8 per cent solution of alcohol by volume. Another measurement was made 10 minutes previous to the last measurement quoted, and also after 8 c.c. of alcohol had been introduced. At this time the minute output was 333 c.c., the blood pressure, 185/115, and the external work of the two ventricles, 2.0 calories. The oxygen consumption of the heart, as read from the spirometer curve, and after deduction of the amount consumed in the lungs, was 274 calories, giving a calculated mechanical efficiency of 0.7 per cent. Fifteen minutes after the last alcohol had been introduced into the system, 4 c.c. of digilanid C were introduced into the reservoir. Ten minutes after this the blood pressure was 225/115, and the minute output had risen to 575 c.c. The calculated external work of the left ventricle was therefore 4.1 calories. The oxygen consumption of the heart alone was 286 calories, giving a mechanical efficiency of 1.4 per cent. The volume of the ventricles was now 5 c.c. less than at the beginning of the experiment, but we must take into consideration that there was a slight leak in the cardiometer. This experiment shows that alcohol reduces the mechanical efficiency of the heart at the same time that the heart dilates, and that digilanid C makes the mechanical efficiency even better than at the start of the experiment.

The one experiment with diphtheria toxin was not completely satisfactory. We had at our disposal a comparatively weak diphtheria toxin ($L = 0.035$). Moreover, as is frequently the case with diphtheria toxin,

an arrhythmia was produced. The rate became rapid and the beating irregular. The results are never quite as clear-cut when arrhythmias complicate the picture. The heart-lung preparation, which came from a dog weighing 18 pounds, seemed to be in excellent shape. The work of the ventricles before diphtheria toxin was given was 3.1 calories. The oxygen consumption of the heart was 183 calories, giving a mechanical efficiency of 1.7 per cent. One hundred eighty c.c. of the diphtheria toxin were put into the reservoir, and, 41 minutes later the work of the heart in calories was 3.2, and the oxygen consumption of the heart for one minute was 287 calories. This gave a mechanical efficiency of 1.1 per cent, or approximately a 35 per cent diminution in mechanical efficiency. Four c.c. of digilanid C (0.8 mg.) were injected into the reservoir, and, 13 minutes later, the work of the ventricles was 3.3 calories and the oxygen consumption of the heart for one minute was 223 calories, giving a mechanical efficiency of 1.5 per cent. Five minutes later the work of the ventricles and the oxygen consumption were the same. We suspect that auricular fibrillation was present but could not settle the question definitely.

We attempted one experiment with potassium chloride, but we were unable to calculate the work of the ventricles accurately after giving the potassium chloride because the rate became very slow and the beating was very irregular; the cardiac output measurements were very unequal, and we felt that it was impossible to make an accurate estimation of the work of the ventricles because of the impossibility of obtaining accurate mean blood pressure values.

These experiments show that, when the heart muscle is rendered hypodynamic by a poisoning agent, the first effect is to reduce the ratio of external work that can be performed when a given amount of oxygen is consumed in the combustion of energy releasing materials. Consequently, the heart is not able to pump as much blood per beat, if the blood pressure is kept constant, because the amount of external work must decrease. This leads to retention of blood in the ventricles at the end of systole. Blood is flowing from the periphery with the same velocity, for the moment, as before the heart muscle started to fail, and, in consequence, there will be an increased amount of blood within the ventricles and some rise in the intraventricular pressures, as well as in the auricular pressure at the end of diastole. A rise in auricular pressure will lead to increased venous pressure. The rise in intraventricular pressure at the end of diastole leads to increased stretching of the heart muscle fibers and increased diastolic volume. The increased diastolic volume results in an increased oxygen consumption, or an increased consumption of energy releasing materials in the heart muscle. In consequence, there will be an increased amount of energy available for external work after dilatation has been effected. Ultimately there is a tendency toward restoration of the amount of external work performed by the heart muscle, but at the cost of increased oxygen consumption, in-

creased diastolic volume, and increased venous pressure. If the heart muscle becomes only slightly hypodynamic and the blood pressure remains constant, increased diastolic volume will be sufficient to keep up the stroke output at approximately its previous value. But with higher degrees of injury to the heart muscle, the consequent rise in venous pressure is not sufficient to dilate the heart enough so that it can eject the same amount of blood as previously, even with increased oxygen consumption. Under these circumstances the stroke and minute output, as well as the external work of the heart, diminish considerably. By increasing the input of blood, and thereby raising the venous pressures to very high values, we can, in the heart-lung preparation, frequently keep the stroke and minute output constant, despite considerable poisoning of the heart muscle fibers, but at the cost of a very marked increase in oxygen consumption.

The primary effect of digitalis is again demonstrated to be that of an increase in the mechanical efficiency of the heart, as first stated by Peters and Visseher,⁶ and when this occurs the heart is able to pump more blood in its dilated state. In consequence, part of the residual blood in the ventricles, as well as in the venous reservoirs, is pumped out, the dilatation recedes, and the venous pressure declines. Digitalis may restore the previous condition, or there may be some increased venous pressure and dilatation after the digitalis effect is complete.

CONCLUSIONS

The cardinal features of spontaneous heart failure or that produced by chloroform, chloral hydrate, alcohol, and diphtheria toxin are (a) a decrease in the mechanical efficiency of the heart; (b) dilatation of the ventricles; (c) a rise of venous pressure in the left and right auricles; and (d) a tendency toward a decrease in the minute output of the ventricles.

When the heart is poisoned with potassium chloride the ventricles dilate, the venous pressure rises in the left and right auricles, and there is a tendency toward a decrease in the ventricular output.

In one experiment in which the diastolic volume and the oxygen consumption were kept constant, there were a decrease in the mechanical efficiency of the heart, a tendency toward a decrease in the minute output of the ventricles, as well as the mean blood pressure, and a rise of venous pressure in the left and right auricles.

Digilanid C (Cedilanid), a digitalis glycoside, increases the mechanical efficiency of the heart provided the heart failure has not been allowed to go too far. It increases the cardiac output, decreases the ventricular dilatation, and decreases the venous pressures.

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DISCUSSION

DR. GEORGE HERRMANN, Galveston.—These experiments of Drs. Fahr and Buehler are very interesting with respect to the progress of the mechanics of heart failure. In the early work that we reported on the chemistry of heart failure, we did experiments somewhat similar to those which Dr. Fahr has presented, except that we carried the hearts to spontaneous exhaustion and then studied the changes in the chemistry of the heart muscle. It must be remembered that we are dealing in these animal experiments with normal hearts that have a good coronary arterial system. Such relatively young hearts might possibly compensate by increased oxygen consumption, which could not be made available to the heart muscle in the presence of an impaired coronary circulation.

We cannot apply Dr. Fahr's and Dr. Buehler's observations directly to our human problems because it seems to us that in most cases a deficiency in oxygenation of the heart muscle is a primary factor in myocardial insufficiency. Chemical change is an equally large factor, at any rate, and seems to us more important than the mechanical factor.

Diphtheria toxin is a rather unusual cause of failure of the human heart. Of course, the heart which is the seat of valvular disease is under strain, but the chief factor in the hypertensive heart is one of decreased circulation or decreased oxygenation. We have the conception that the trouble begins with the deficiency in oxygenation, and that the efficiency of the heart suffers for that reason.

Ruskin pointed out in these experiments that there is both forward and backward failure. The backward failure is that which Dr. Fahr and Dr. Buehler have demonstrated in the rise of venous pressure. The forward pressure was not measured so extensively. The authors stress again the mechanical factor of increased venous pressure as an index of heart failure, as we conceive it clinically.

There are those, of course, who have a conception of heart failure of the forward type, in which venous pressure does not necessarily rise as it did in the experiments that were quoted.

It would be interesting to have, along with these observations on mechanical changes, data concerning the chemical changes that go on in the heart muscle as the mechanical efficiency decreases. I am sure that there would be an index loss of creatine; that is, digitalis sometimes helps in that way to support or exert its tonic effect on the myocardium.

DR. HAROLD E. B. PARDEE, New York.—I am very glad to hear that Dr. Fahr has started on an investigation of heart failure, because I feel that we very definitely need to have a clinical definition of heart failure that is more adequate than the one now being used. He stated that he is progressing from his experimental work to a clinical application.

It has been very disturbing to see the variable meanings that have been given to the term "heart failure" by different writers. Some apply it only to the most severe types, in which the patient is reduced to the state of being in bed. Others apply it to lesser grades of heart failure, when the patient is not particularly ill, but may have râles at the bases of the lungs posteriorly.

I think the important thing to stress is Dr. Fahr's statement that when the heart begins to fail in its mechanical efficiency, that is the beginning of heart failure. It seems to me that this also marks the beginning of human heart failure. In other words, when the patient is unable, without producing cardiac symptoms, to undertake any physical effort that he had previously been able to make without such symptoms, this indicates the beginning of his heart failure.

What we need and what I hope Dr. Fahr will produce for us is a useful clinical definition.

A committee of the New York Heart Association some years ago tackled this problem and divided heart failure into four grades, calling them Classes 1, 2, 2A, and 3. These titles were later changed to Classes 1, 2, 3, and 4, respectively. This is a measure of heart failure which has been of some use, but it has for some reason removed the emphasis from the underlying condition of heart failure and has not indicated when one should begin to use this term. I believe it is important to use it at the very beginning, at the first sign of the heart's being overtaxed.

DR. GEORGE FAHR, Minneapolis.—I am very glad that I can throw some light on the points that the two previous speakers brought up. Dr. Herrmann talked about the probable difference in the mechanism in coronary disease, when one starts out with a deficiency of oxygen.

Those who have worked for years with the heart-lung preparation could have said, "You don't need to worry about that." When one decreases the supply of oxygen going to the heart muscle with the heart-lung preparation, one gets exactly the same thing as with poison. As venous pressure goes up and dilatation takes place, oxygen consumption increases.

I can report some work, not my own, which has been largely completed, and which shows that this law holds exactly, no matter how the experiment is done. In these very accurate experiments, one can greatly decrease the amount of oxygen going to the heart. It begins to consume tremendously increased amounts of oxygen as it dilates. The supply of oxygen is greatly diminished in those very fine experiments, done in the physiologic laboratory of Dr. Visseher.

With oxygen deficiency the heart consumes more oxygen. Clinicians think that this is a paradox. It sounds like a paradox, but it has to do with the intimate muscle mechanism that takes place when the heart becomes hypodynamic.

The way we carry out this type of experiment on our patients is as follows: We measure the cardiac output, the blood pressure, the venous pressure, and the diastolic volume, which, of course, varies with oxygen consumption. The cases which we have studied in largest degree, because there are so many in our hospital, are cases of coronary disease. These patients come in with heart failure, dilatation of the heart, usually with decreased stroke and minute output, and high venous pressure. We put them to bed and give them digitalis. The dilatation recedes, the oxygen consumption diminishes, and usually work increases. The arterial pressure remains constant and the venous pressure goes down. What is true of heart failure in coronary disease is also true of other kinds of heart failure, such as rheumatic heart disease with valvular

defects. We have all kinds of heart disease, and it is always the same as in the animal experiments with the poison. The patients come in with dilated hearts. After rest and digitalis the dilatation goes down, work increases, and mechanical efficiency goes up.

We have gone over to our dispensary, where we have people with coronary disease, with mitral disease, with hypertension, and with aortic disease, but all we can find is an enlarged heart. They have no symptoms, no dyspnea. The venous pressure is normal, but the vital capacity frequently is low, which means, of course, that there is some left-sided heart failure. But, we have had some patients who had very little decrease in vital capacity. Whether we are justified in saying that there is no venous pressure rise in the left side, I don't know. We have had some patients with very little dilatation of the heart, which is extremely interesting. After digitalis the same thing occurs in these hearts. The diastolic size of the heart diminishes. There is no effect on the venous pressure because it was normal in the first place. But, the mechanical efficiency, or work divided by the oxygen consumption, increases in these hearts which are not demonstrably failing. These patients are running around. They are not doing their usual work, but they are living at home and are not seriously incapacitated.

Dr. Pardee said that he wanted a definition which a clinician could use. I have used the above as a clinical definition now for two or three years. Of course, one cannot define heart failure by means of percussion and auscultation alone. One has to have certain instruments with which to do it. But the investigating clinician can study heart failure on his patients just as easily and almost as accurately as we can in the laboratory.

We took our nurses and our interns with normal hearts and did the same thing. We measured the diastolic volume, the stroke output, and blood pressure. Their mechanical efficiency under digitalis decreases.

The effect of digitalis on a normal heart is exactly opposite to what it is on a hypodynamic heart.

HEMIPLEGIA FOLLOWING BRADYCARDIA AND CARDIAC STANDSTILL

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THE cerebral manifestations of bradycardia and cardiac standstill are well known. The symptoms are vertigo, faintness, and loss of consciousness, with convulsive seizures and death, depending on the degree of slowing, the length of the periods of standstill, and the physical state of the cerebral arteries. Stokes¹ reported that transient hemiplegia may be a sequel to cardiac standstill. Cardiac standstill of less than two seconds causes a feeling of faintness; of more than four seconds, syncope; and, with longer periods of standstill, from twenty to forty seconds, convulsive movements occur and the respiration becomes slow and the skin pale. Patients usually do not recover from attacks of cardiac standstill which last longer than one to two minutes. Levine and Matton² reported a case of Adams-Stokes syndrome caused by ventricular fibrillation and ventricular asystole of five minutes' duration. This was followed by complete standstill of the ventricles for seventy-nine seconds, and, after the intracardiac injection of adrenalin, rapid ventricular contractions reappeared. The phenomena of syncope are caused by cerebral anemia. There are many causes, such as ordinary fainting attacks, postural hypotension, hypersensitiveness of the carotid sinus, cardiac standstill as a result of A-V dissociation, paroxysmal tachycardia or ventricular fibrillation, and aortic stenosis.

This report concerns two patients who had syncope attacks associated with (1) bradycardia and (2) cardiac standstill, and subsequently developed hemiplegia. No other identical cases have been found in the literature, but two cases of A-V nodal rhythm and syncope attacks have been reported.^{3, 4}

CASE REPORTS

CASE 1.—R. P., a 36-year-old housewife, was admitted to Lakeside Hospital July 4, 1934, with a history of palpitation and fainting attacks for one month. On the day of admission she had an attack of syncope, with convulsions. During this attack there was no radial pulse. During the next hour several more attacks occurred.

Past History.—The patient had had diphtheria and pneumonia in childhood, and hysterectomy five years previously.

Physical Examination.—She was a well-developed and well-nourished white woman, in no discomfort. The heart was normal in size and there were no murmurs. The heart rate was 70 per minute and the rhythm was apparently normal. The peripheral arteries were normal and the blood pressure was 120/80. The edge of the liver was barely palpable. The examination was otherwise negative.

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Laboratory Data.—The urine was normal; leucocyte count, 17,450; erythrocyte count, 4,970,000; hemoglobin, 93 per cent; blood Wassermann reaction, negative.

The electrocardiograms showed:

July 4, 1934, A-V nodal rhythm (rate 62).

July 5, 1934, A-V nodal rhythm (rate 51) (Fig. 1).

July 9, 1934, A-V nodal rhythm (rate 75).

Fluoroscopic examination of the aorta and heart revealed no abnormalities.

Subsequent Course.—During the following years the patient had occasional spells of vertigo and syncope, and her heart rate remained about 48 per minute. On March 29, 1938, she complained of a feeling of weight in the epigastrium on exercise. Her heart was normal in size and there were no murmurs. The blood pressure was 172/90, and the heart rate was 36 per minute. The electrocardiogram showed A-V nodal rhythm, but was otherwise normal. On May 18, 1938, while eating lunch, she suddenly lost the use of her left side and became stuporous. There were no convulsive seizures. She was readmitted to Lakeside Hospital May 22, 1938.

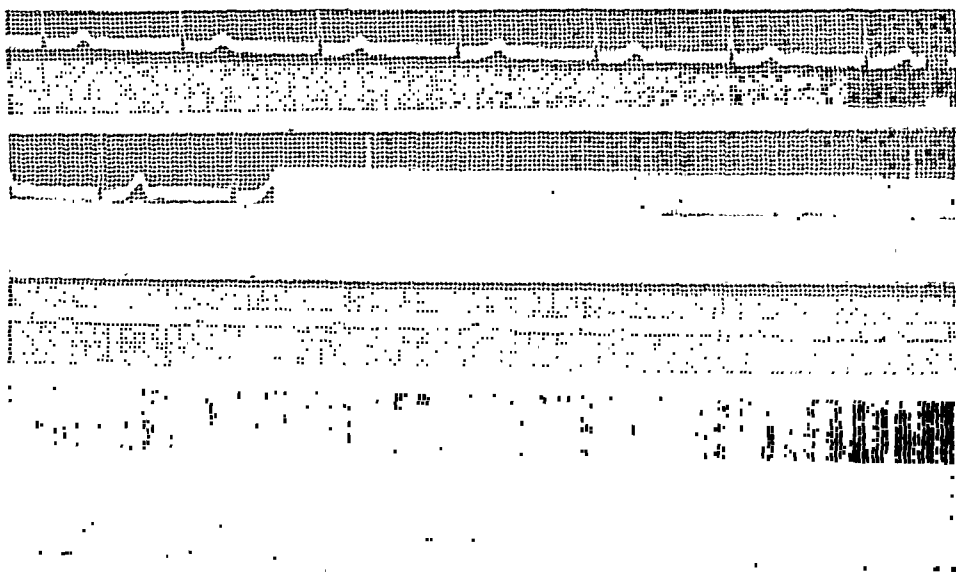


Fig. 1.—A-V nodal rhythm; rate, 51 per minute.

Physical Examination.—The patient was in a stupor. The heart was normal in size and there were no murmurs. The rate was 35 per minute and was rhythmic. The blood pressure was 150/90. The left corneal reflex was absent. Both optic discs were normal. The left side of the face was paralyzed, the occipitofrontalis to a lesser degree. The left arm and leg were completely paralyzed. Mayer's reflex was absent in the left hand but present in the right. The left abdominal reflex was absent. Babinski's sign was present on the left. Marked hyperesthesia was present over the left arm. There were no sensory changes over the left leg.

Laboratory Data.—Roentgenograms of the skull showed that the sella turcica was normal in size and configuration. There was no evidence of any pathological process in the bones. The electrocardiogram showed A-V nodal rhythm (rate, 35). The spinal fluid was normal in all respects.

The patient has survived, and the cause of the hemiplegia is highly speculative. The patient is young and has no signs of peripheral arteriosclerosis, or arteriolosclerosis, or any other disease that might have caused the condition. During the past three years the paralysis has gradually receded, and now only slight paresis remains. The A-V nodal rhythm has continued, and the rate is stabilized at

approximately 32 per minute. It is suggested that the diphtheria which occurred in childhood was the cause of the disease of the sinus node.

CASE 2.—G. S., a 27-year-old woman, a secretary, was first seen March 17, 1934, complaining of attacks of headache and nausea of thirteen months' duration. A few days previously she had had a fainting attack which lasted one minute. Her pulse rate was 40 per minute.

Past History.—She had had diphtheria at the age of 5 years, at which time she was given antitoxin.

Physical Examination.—She was a well-developed and well-nourished white woman. The heart was normal in size; there was a soft systolic murmur at the apex. The peripheral arteries were soft, and the blood pressure was 144/80.

Electrocardiogram.—2-1 A-V block; auricular rate, 80, ventricular rate, 40. The record was otherwise normal.

Subsequent Course.—On Sept. 11, 1935, she had two attacks of syncope; her blood pressure was 160/80.

Electrocardiogram.—Complete A-V block; auricular rate, 84, ventricular rate, 41. The patient was given ephedrine sulphate in a dose of 0.025 Gm. three times a day.

Jan. 17, 1938.—The patient was admitted to Lakeside Hospital with a complaint of numerous syncopal attacks since the last observation. These attacks occurred without premonitory symptoms, lasted about one minute, and were frequently associated with convulsions, during which she had often fallen and injured herself.

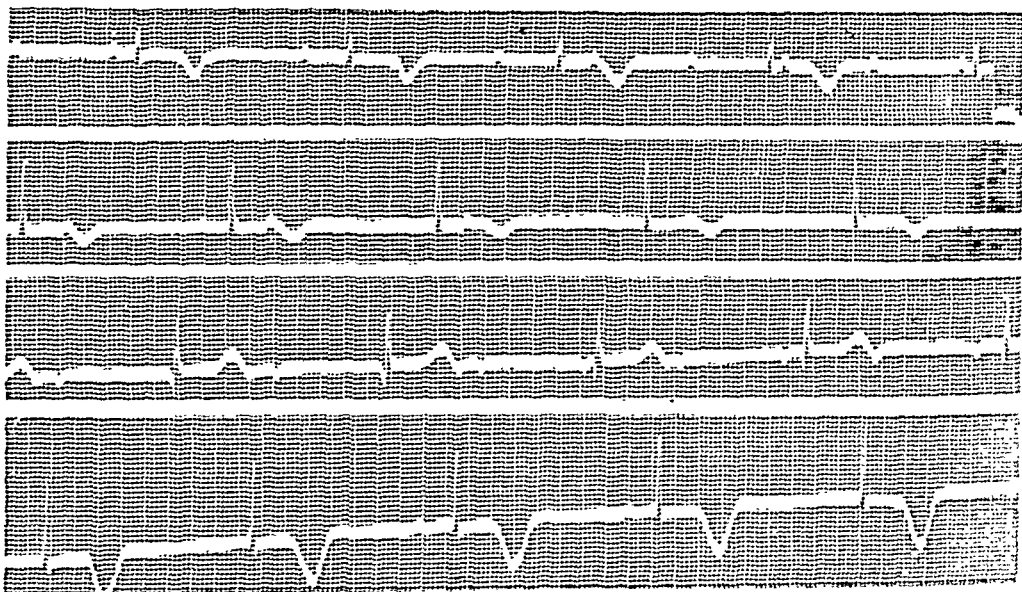


Fig. 2.—Complete heart block. Auricular rate 73; ventricular rate 33. T_1 , T_2 , and T in IV R are sharply negative.

Physical Examination.—There was nothing significant except the bradycardia (rate, 38) and the blood pressure (105/70).

Electrocardiogram.—Complete A-V block; auricular rate, 73, ventricular rate, 33. T_1 was sharply negative and T_2 was sharply elevated (Fig. 2).

On the sixth hospital day the patient had a Stokes-Adams attack, lasting one and one-half minutes. On the seventh hospital day another attack occurred, lasting one minute. On the eighth hospital day the patient developed an acute streptococcal throat infection which was successfully treated with sulfanilamide. An attack occurred on this eighth hospital day, and on the ninth day she had a long attack, lasting about thirty minutes, during which the heart rate fell to about

20 per minute and the pulse became almost imperceptible. On the eleventh day another attack occurred, lasting one minute. Adrenalin in a dose of 0.5 c.c. of a 1:1000 solution was given subcutaneously. A few minutes later a second attack occurred, lasting about three minutes, during which no heart sounds could be heard and respirations ceased. Artificial respiration was started and 1.0 c.c. of adrenalin was given by intracardiac injection. One-half minute later the radial pulse could be felt but the heart was rapid and arrhythmic. Later in the afternoon an electrocardiogram showed complete A-V block (auricular rate, 120, ventricular rate, 57). On the next day the complete block was interrupted at intervals by short runs of ventricular tachycardia.

On the fourth day after the long attack of syncope, the patient had an attack lasting four to five seconds, following which she developed a combined (receptive-expressive) aphasia and right-sided hemiplegia and hemianesthesia. Seven days later slight movement returned on the right side, and convalescence progressed. Adrenalin, in a dose of 0.5 c.c. of a 1:1000 solution, was given hypodermically for acute attacks, and ephedrine sulphate was given by mouth (0.025 Gm.) four times daily.

During the following year the patient regained partial use of the right arm and right leg, but there was no recovery of sensation. She continued to have attacks of syncope one to two times a week, and later four to five times a day. Benzedrine sulphate in a dose of 10 mg. was given three times daily, and the attacks occurred less frequently. The attacks again recurred at more frequent intervals and she was readmitted to Lakeside Hospital May 31, 1939, in a semi-comatose state; she was having frequent Stokes-Adams attacks. She was given 1 c.c. of a 1:1000 solution of adrenalin, and had but three very brief attacks during the eleven days of hospitalization. She was then given 0.025 Gm. of propadrine hydrochloride three times daily, but continued to have frequent attacks of syncope. She died in an attack on Oct. 30, 1939.

POST-MORTEM OBSERVATIONS

Heart.—The heart weighed 210 grams. The gross appearance was normal. No thrombi were seen in any of the chambers. Histologic examination showed an increase in the amount of connective tissue in the region of the Bundle of His.

Brain.—The brain after formalin fixation weighed 1120 grams, and was of firm consistency. There was an area of softening of the left hemisphere in the distribution of the Sylvian artery. This involved the superior and part of the middle temporal convolutions, the inferior frontal cortex at the level of the temporal pole, the lower central cortex, the insular cortex, part of the supramarginal gyrus, and the anterior part of the angular gyrus (Fig. 3). Coronal sections revealed an old, healed area of encephalomalacia composed of yellowish-gray tissue containing an irregular network of connective tissue strands which formed either dense bands or spongy, multilocular, cystlike cavities. The lesion involved the gray and white matter of the third frontal convolution at the level of the genu of the corpus callosum and became more extensive caudally. The inferior portion of the head of the caudate nucleus, the internal capsule between this and the putamen, the external portion of the globus pallidus, and the insular cortex were destroyed (Fig. 4). Further posteriorly, the degeneration lay lateral to the thalamus and involved the white matter and cortex of the parieto-occipital lobe. It terminated at the level of the tip of the posterior horn of the lateral ventricle. The left lateral ventricle was widened. A portion of the anterior superior aspect of the vermis of the cerebellum was softened. Degeneration of the projection tracts had resulted in atrophy of the peduncle and pons on the left and of the pyramid of the medulla on the right.

There was no evidence of vascular disease, vascular anomaly, or embolism or thrombosis of the circle of Willis, of the left middle cerebral artery, or of that portion of the internal carotid artery which was removed with the brain at autopsy.

Histologic Examination.—Corresponding areas from the two hemispheres were removed, and the sections stained by the Nissl method. Apart from the area of softening described above, the changes in the cortex were identical on the two sides. The ganglion cells were normal except for scattered, shrunken cells, and

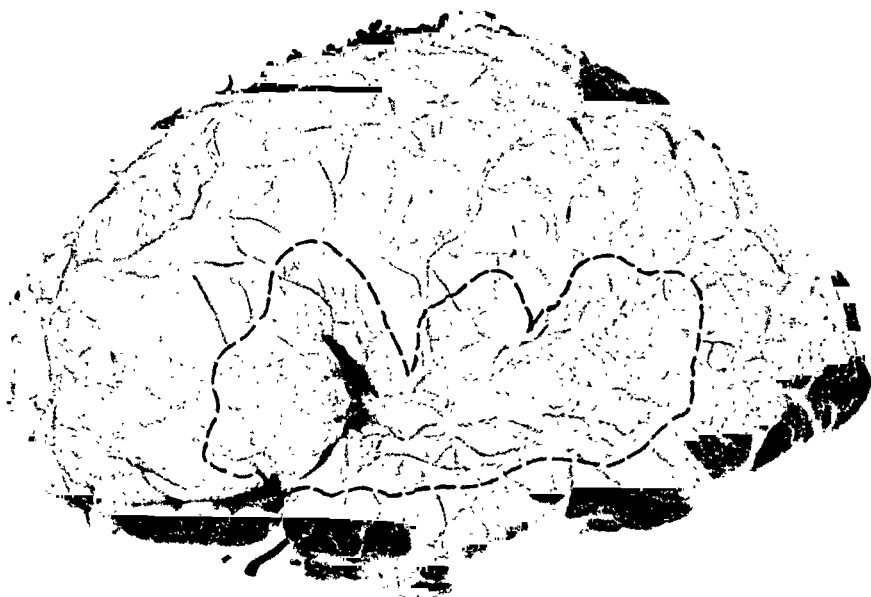


Fig. 3.—Left hemisphere. Broken line shows area of softening visible on the surface.



Fig. 4.—Coronal section of brain showing area of encephalomalacia.

there were no diffuse or focal cellular defects. Some of the small cortical arteries were thickened and had hyalinized walls. The type of cell changes in the cortex resembled those which occur in prolonged or chronic illness. In the area of gross softening the parenchymatous elements were replaced by a network of fibrous and glial tissue which contained compound granular cells and debris.

DISCUSSION

The cause of the encephalomalacia was probably thrombosis of the internal carotid artery in the carotid canal or cavernous sinus. The common carotids pulsated during life but the carotids were not explored at autopsy. Saphir⁵ has emphasized the importance of searching for obstruction of the internal carotid artery in the carotid canal and cavernous sinus in cases of encephalomalacia when the obstruction is not found in the middle cerebral artery or in that portion of the internal carotid that is removed with the brain.

The distribution and type of lesion in the brain were similar to those described after obstruction of the middle cerebral artery,⁶ carotid ligation,⁷ and occlusion of the internal and common carotid arteries.^{8, 9}

That the lesion was not caused by a generalized slowing or stoppage of blood flow is confuted by the lack of evidence of anomalies of the circle of Willis and by absence of ischemic changes in the cerebral cortex apart from the area of gross softening.

If there had been generalized ischemic damage to the cerebral cortex in this case it would still be difficult to explain why only that part of the brain supplied by the left middle cerebral artery was severely damaged. Experimental evidence^{10, 11, 12} and observations on man¹³ indicate that the ganglion cells of the cerebral cortex may be permanently damaged by anoxia for a period of about five minutes. There is evidence^{14, 15} that the vulnerability of the neostriatum corresponds to that of the cerebral cortex, but the vital centers in the brain stem have greater resistance. Short nonlethal periods of oxygen deprivation may give rise to syncope, convulsions, or impaired mental function.

The autopsy observations ruled out the possibility that the cerebral softening was caused by embolism arising from a thrombus formed at the site of intracardiac injection, for no injury of the heart wall was found. No thrombi were found in the left ventricle. They also ruled out the possibility of thrombosis in the middle cerebral artery. The strictly focal character of the encephalomalacia and the absence of anomalies of the vessels of the circle of Willis are arguments against the idea that the damage resulted from the generalized cerebral anoxia during the long period of cardiac asystole.

SUMMARY

Two cases of hemiplegia are reported; one patient had auriculo-ventricular rhythm, and the other, complete heart block. The latter patient came to autopsy, and widespread encephalomalacia in the area

supplied by the middle cerebral artery was found. No thrombi were found in the arteries. The obstruction may have been in the artery in its course through the carotid canal or the cavernous sinus.

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Clinical Reports

BILATERAL MISSED BLOCK

REPORT OF A CASE IN WHICH THERE WAS LEFT BUNDLE BRANCH BLOCK
DURING LIFE, WITH AUTOPSY

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MICROSCOPIC study in cases of bundle branch block has resulted in contradictory results. Seemingly convincing evidence has been obtained to support both the classical and the new concepts of bundle branch block. One fact seems certain; namely, that the lesions almost always affect both branches of the bundle of His. It is also clear that many of the studies have been based upon an erroneous concept of the normal anatomy of the conduction system. Ever since the work of Tawara and Mönckeberg, it has been assumed that the two branches of the bundle of His remain isolated in their whole course along the inter-ventricular septum, or at least in the first part of this course. But high connections unite the branches and the trunk with the ventricular musculature, and destruction of both branches is compatible with normal auriculoventricular conduction. The association of normal auriculoventricular conduction time with destruction of both branches is a condition that has been described as "bilateral missed block." The case presented here is reported because, in the presence of left bundle branch block (new nomenclature), there was complete destruction of both branches, while high connections united the trunk with the ventricular septal musculature.

CASE REPORT

The patient was a 71-year-old man who had shown evidence of left ventricular failure for six or seven years, and of right ventricular failure for six months. Six months earlier he had been examined in another hospital, where the blood pressure was found to be 170/110, and the blood urea nitrogen 35 mg. per 100 c.c. On admission the patient had severe dyspnea, emphysema, and pulmonary congestion. The left ventricle was much enlarged, gallop rhythm and pulsus alternans were present, and the blood pressure was 130/85. The fundi showed nothing of significance. The blood Wassermann reaction was negative, the figures for blood sugar and urea nitrogen were 85 mg. and 18 mg. per 100 c.c., respectively, and the blood cell count was essentially normal. The electrocardiogram showed auricular flutter, with 4:1 block, a ventricular rate of 75 per minute, and occasional premature ventricular beats. The conduction time from the last flutter wave to the initial deflection, as measured in Lead I, was 0.14 second. QRS measured 0.14 second, was of increased voltage,

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nections, designated as such by Mahaim in 1932, are constant in the human heart, as well as in the heart of the cat, dog, rabbit, pig, and sheep. They are also present in the calf's heart, although Tawara, who studied the bundle of His particularly in this animal because of the marked specific appearance of the bundle there, thought that the branches were completely isolated. Yet it is possible to demonstrate these high connections in the calf's heart also, although it should be admitted that they are much less frequent than in the heart of the cat and the rabbit. Recent studies on this aspect of the comparative anatomy will be published soon by Mahaim and Winston. Obviously, in dealing with the problem of bundle branch block it is important to realize that the common trunk, as well as both branches, is in connection with the ventricular septal myocardium. Any physiopathologic studies with respect to conduction through the diseased bundle of His must include a consideration of these high connections. This is a difficult task. It is customary, in studying the anatomic relations of the branches, to stain only one out of five, ten, or even twenty of the 5,000 to 6,000 sections, according to the nature of the case or the different levels under study. But in order to detect these higher connections, consecutive slides from points where these connections might be expected must be stained and studied without interruption.

When Mahaim examined, in 1932, a case of so-called bundle branch block in which the duration of the QRS complex was extremely long, his findings were surprising and even paradoxical. During life the atrio-ventricular conduction time had been perfectly normal, but microscopic study revealed complete destruction of both branches in this region. The excitation wave had passed exclusively through the high connections. This condition has been described as "bilateral missed block." Experimental studies along this line were carried out by Rothberger and Mahaim, in 1935, and the microscopic observations made during these studies will be published soon (with Winston). It is interesting that, as early as 1908, Biggs⁵ observed lack of constancy in the A-V block which followed destruction of both branches in the rabbit's heart.

Bilateral missed block is not associated with the electrocardiographic features of A-V block, although both branches are destroyed. The duration of the QRS complex is much increased because the excitation wave, in order to reach the papillary muscles and the apical region, follows an atypical path through the musculature of the interventricular septum. The longer the lesions of the small branches along the septum, the larger the QRS area will be. Our patient had auricular flutter with a variable rate of A-V conduction; hence the A-V conduction time could not be ascertained. However, the absence of complete A-V block in the presence of complete interruption of both bundle branches justifies classifying this case as one of "bilateral missed block."

SUMMARY

1. Contrary to common belief, the two branches of the bundle of His are not isolated in their course along the interventricular septum. Connecting branches as high as the top level of the musculature occur in the hearts of men and animals. A continuous series of stained sections must be studied in order to demonstrate these fine connections. In most instances the common trunk of the bundle of His is likewise connected with the ventricular myocardium. Because of the presence of these high connections, the A-V conduction time may be normal in spite of destruction of both branches. This has been designated as "bilateral missed block."

2. A case is reported in which, during life, there were auricular flutter and so-called left bundle branch block (new nomenclature). On microscopic examination both branches were found to be destroyed and the trunk was seriously damaged, but it was possible to demonstrate direct fiber connections with the ventricular myocardium. The excitation wave must have passed these high connection fibers. The absence of complete A-V block in the presence of complete interruption of both bundle branches makes this a case of "bilateral missed block."

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A CASE OF THROMBOANGIITIS OBLITERANS IN WHICH A STENOSIS VESSEL MURMUR WAS RECORDED THROUGH THE ESOPHAGUS

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THROMBOANGIITIS obliterans was described by Buerger, in 1908, as a chronic disease with inflammatory involvement of the blood vessels. Stenosis or occlusion of the vessel is caused by proliferation of the endothelium or by thrombosis, and disturbed circulation of the blood gives rise to various symptoms.

Formerly it was believed by a number of investigators that the involvement of the vessels was confined to certain peripheral arteries, particularly to the arteries of the extremities, but recently it has been observed that it also occurs in central vessels, such as the aorta and its main branches.

One of the main symptoms of thromboangiitis obliterans is disappearance of the pulsation in the involved artery; it is often accompanied by an ophthalmologic abnormality, such as cataract or abnormal anastomosis of retinal vessels.

Onishi,¹ a Japanese ophthalmologist, reported, in 1907, a case of a vascular disease with loss of vision and disappearance of the radial pulsation. Nakajima² reported the same type of case, in 1920; subsequently, similar instances have been observed by various investigators in Japan, including Yoshikawa,³ Minogoshi and Uchiyama,⁴ Tomita and Higashi,⁵ Nagashima and Kitamoto,⁶ Hayashi and Nishimura,⁷ Dodo,⁸ and Sato.⁹

In thromboangiitis obliterans, arteriographic examination has been regarded as necessary if one is to ascertain the degree of involvement. When stenosis or occlusion exists in an artery of the extremities or brain, the involved region may be revealed clearly by the arteriogram, but we may not apply this method to central arteries like the aorta or its main branches. Without arteriographic examination, we are obliged to judge the degree of obstruction solely by ordinary physical examination and symptoms.

I have already reported¹⁰ a new method of recording heart sounds through the esophagus, and stated that an aortic murmur may be heard at a distance of 25 to 28 cm. from the front teeth, where the aortic arch is close to the esophagus.

Recently we examined a patient with thromboangiitis obliterans who had no pulsation of the radial arteries on either side. We were not

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able to make an arteriographic examination, but succeeded in recording a loud vessel murmur through the esophagus, which indicated inflammatory involvement of the aorta.

We believe that the recording of a murmur through the esophagus at the top of the aortic arch is one of the important signs of stenosis of one of the great arteries situated close to the heart.

Whether or not a vessel murmur may be recorded through the esophagus in cases of thromboangiitis obliterans or angiitis rheumatica has not been reported. The following is such a case.

REPORT OF CASE

H. H., a Japanese woman, aged 26 years, was admitted to our clinic Feb. 19, 1940, complaining of visual disturbances and disappearance of the radial pulsation.

Family History.—Her grandfather and grandmother died of apoplexy.

Past History.—It was stated that she had had no serious illness during her childhood. She married at the age of 23 years. In January, 1939, she consulted a physician who made a diagnosis of spondylitis dorsalis and pregnancy of four months' duration. Therapeutic abortion was recommended, and she had the operation. There was no history of syphilis.

Present Illness.—The patient complained of diminution of vision in both eyes, particularly the left, in April, 1938. Ophthalmologic treatment somewhat improved her vision. Thereafter she often complained of dizziness, and sometimes she became faint. In December, 1939, her vision failed again, and she had temporary dysarthria and motor aphasia. She consulted an ophthalmologist, who found a cataract in her left eye. At that time the examiner could not palpate any pulsation in the radial arteries, but the patient stated that she had once palpated it herself.

Condition on Admission.—The patient was small, slender, and slightly undernourished. She was pale, but neither cyanosis nor gangrene was present in the extremities. Neither radial pulse was palpable. The carotid pulses were small. No pulse could be felt in either temporal, axillary, or brachial artery. The pulse in the abdominal aorta was normal, but that in the common iliaes, femorals, popliteals, and dorsales pedum was diminished in volume.

The chest was normal. The apex impulse was in the fifth intercostal space at the left nipple line. The right border of cardiac dullness was at the midsternal line, the left border at the left nipple line, and the upper border at the fourth rib. A soft, blowing, systolic murmur was heard over the entire precordium. At the pulmonic area and the base it was slightly louder. At the cardiac apex the third heart sound and a faint systolic murmur were heard. The pulmonic second sound was accentuated.

Examination of the lungs, abdomen, and nervous symptoms revealed nothing of importance.

Laboratory Examination.—The erythrocytes numbered 4,930,000, and the leucocytes, 6,400; the hemoglobin was 85 per cent, according to Sahli's method. The urine showed no abnormalities.

Ophthalmologic examination revealed a cataract on the left, anastomosis arterio-venosus retinae coronaria, and diminution of vision in both eyes, particularly the left. The pressure in the central artery was low.

The roentgenogram showed slight, general enlargement of the heart and the aorta. There was no aneurysm of the aorta.

The electrocardiogram revealed right ventricular preponderance and no evidence of myocardial disease.

Microscopic examination of the capillaries in the nail beds of the fingers showed enlargement and marked tortuosity of the arterial and venous vessels on both sides, particularly the left.

The blood pressure was measurable neither by the auscultatory nor palpatory method, because there was no pulsation of the arteries of the upper extremities and no Korotkov sounds could be heard. The blood pressure in the popliteal arteries was 203/150 on the left side, and 190/130 on the right side.

A sphygmogram from the radial artery showed a monoerotic wave with very little amplitude. A sphygmotachogram (by Dr. Tsutsumi, in our clinic) is shown in Fig. 1; it was recorded with extremely high magnification. The blood pressure in the arms and legs was obtained with the help of the sphygmotachogram. In the arms it varied from 40 to 45, systolic, and in the legs it was 132, systolic, on the right side, and 120, systolic, on the left side.

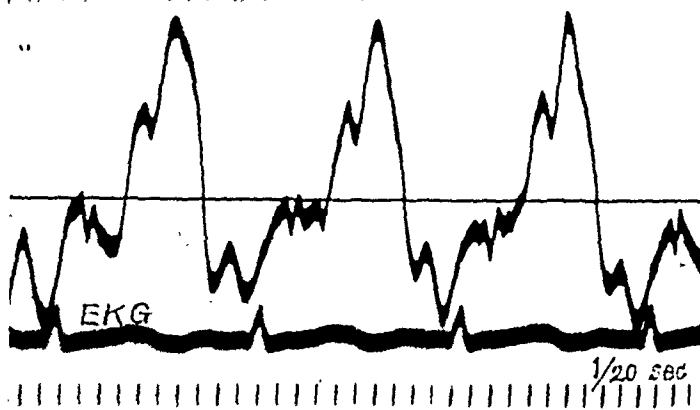


Fig. 1.—Sphygmotachogram from the right radial artery.

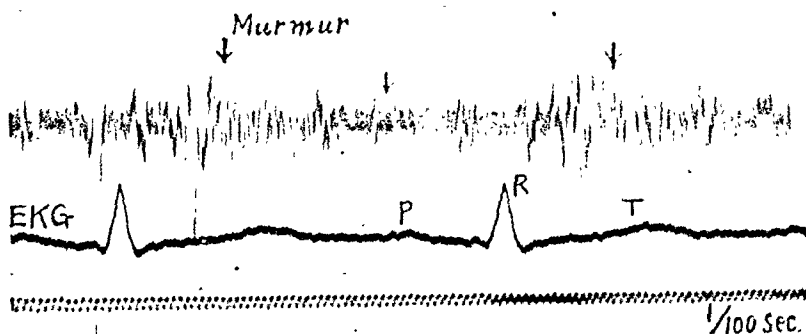


Fig. 2.—Vessel murmur recorded through the esophagus at a distance of 27 cm. from the front teeth. The murmur is present during both systole and diastole.

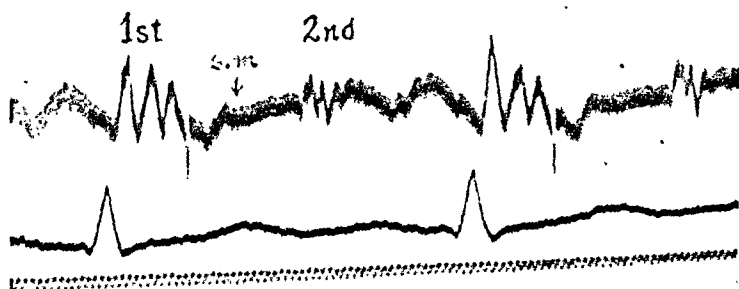


Fig. 3.—The heart sounds recorded through the esophagus at a distance of 27 cm. from the front teeth, to correspond to the left ventricle. Beside the first and the second heart sounds, a systolic murmur is shown as a mere trace.

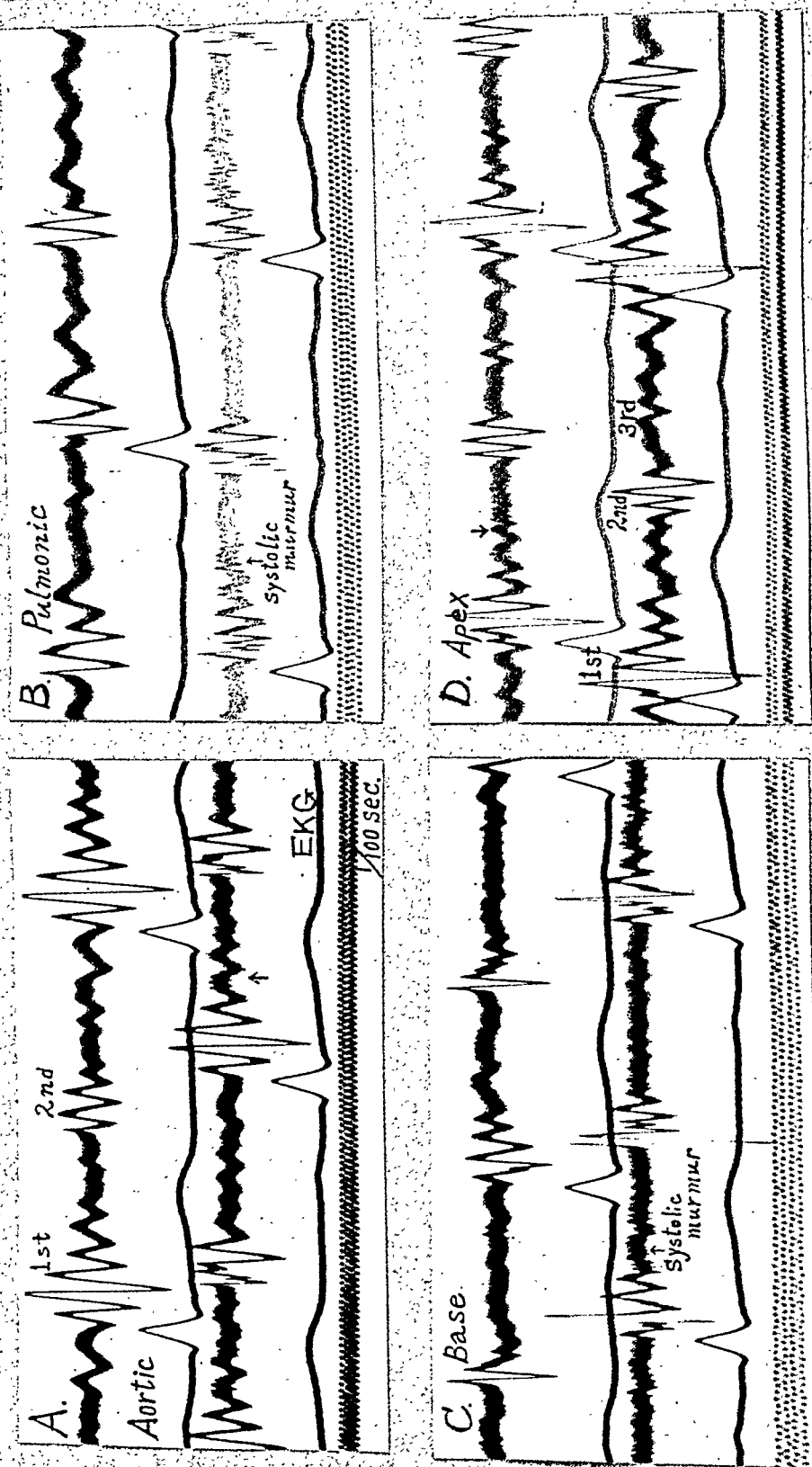


Fig. 4.—The heart sounds recorded over the precordium. (The lower strips in A, B, and C and the upper strip in D were recorded by the use of a high-pass filter. The remaining tracings were recorded without the filter.) Over the aortic area and the apex a systolic murmur is shown as a mere trace. Over the pulmonic area and the base a systolic murmur is fairly well shown. No diastolic murmur is shown in any tracings.

The heart sounds were recorded over the apex, the base, the pulmonic area, the aortic area, and the tricuspid area by means of Koizumi's¹¹ apparatus. This apparatus utilizes high frequency current. It consists of a microphone, an oscillator, a detector, an amplifier, and an oscillograph. The microphone employed by us was a round metal plate with a diameter of 3 cm.; it was insulated by a mica plate. The microphone was connected to the grid of the oscillator. The chest wall is made to oscillate with each cardiac beat, and the change of electrical capacity between the chest wall, which is earthed, and the fixed metal plate is received and magnified; thus the heart sound is recorded by the oscillograph.

For the recording of a vessel murmur through the esophagus, we employed the method previously reported by the writer.¹⁰ We had the patient swallow an insulated metal cylinder (1.5 cm. \times 0.4 cm.), which was connected to the oscillator of Koizumi's apparatus by a fine wire through a rubber tube.

We recorded the sound through the esophagus at a distance of 25 to 28 cm. from the front teeth, and by this means registered a vessel murmur which was far louder than any systolic murmur over the precordium. Fig. 2 shows a vessel murmur from the esophagus at a distance of 27 cm. from the front teeth. It shows a frequency of 120 to 480 per second, and has a large amplitude. The murmur was present during both systole and diastole, and was of maximum intensity during the period of outflow. Fig. 3 is a sound tracing recorded at a distance of 37 cm. from the front teeth. In this tracing a faint systolic murmur is shown, in addition to the first and second heart sounds.

The heart sounds over the precordium are shown in Fig. 4. Over the aortic, tricuspid, and apical areas the systolic murmur was recorded as a mere trace, but over the pulmonic area and the base it was recorded fairly well, with a frequency of 120 to 240 per second. Over the apex the third heart sound was recorded. No diastolic murmur was discovered anywhere over the precordium.

SUMMARY AND DISCUSSION

Clinical and laboratory examination of this patient led us to the conclusion that she had Buerger's disease, accompanied by ocular symptoms. The cataract on the left side was probably caused by disturbed blood flow in the ocular circulatory system. The dizziness, dysarthria, and aphasia of which the patient complained temporarily were thought to be the result of insufficient cerebral blood flow.

By recording the sounds through the esophagus, we detected a loud vessel murmur with high frequencies. Clinical observation led us to think that this murmur was caused by stenosis near the orifices of the innominate, common carotid, and left subclavian arteries, and that this stenosis had been produced by proliferation of the endothelium, or thrombosis. The circulation in the upper half of the body was disturbed by this stenosis, but an abundance of blood flowed in the lower half of the body via the abdominal aorta, thus causing hypertension in the lower extremities and an increased pulsation in the *dorsalis pedis*.

The vessel murmur recorded through the esophagus revealed oscillations of high frequencies. Such a murmur may be produced by stenosis of the aortic isthmus, but, in a case of isthmus stenosis, the pulsation of the arteries in the arm is increased, whereas that in the leg becomes smaller.

In our case, a blowing systolic murmur was heard over the precordium, particularly well at the pulmonic area and the base. The roentgenogram and the electrocardiogram revealed no evidence of congenital heart disease or vascular defects. The hemogram showed nothing abnormal. We concluded that this kind of systolic murmur had nothing to do with heart disease or anemia. In the tracing of the sound through the esophagus at the top of the aortic arch, the vessel murmur showed its maximum intensity during the period of outflow of blood from the ventricle. This systolic murmur was, we believe, transmitted to the entire precordium, and particularly well to the pulmonic area.

CONCLUSION

An interesting case of thromboangiitis obliterans, with inflammatory involvement of the vessels near the aortic arch, is reported. In this case a stenosis vessel murmur was found in the sound tracings which were recorded through the esophagus. For the purpose of locating the region of stenosis in a vessel, arteriographic examination is indispensable, but in a case of angiitis centralis we cannot rely on arteriographic examination. In such a case, we believe, the recording of a vessel murmur through the esophagus aids in diagnosis.

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ACUTE, LOCAL, VENTRICULAR ISCHEMIA, OR IMPENDING INFARCTION, CAUSED BY DISSECTING ANEURYSM

CASE REPORT WITH NECROPSY

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THE clinical and post-mortem earmarks of sudden and permanent occlusion (with myocardial infarction) of one of the main coronary arteries are widely recognized. It is also well known that high-grade, permanent occlusion of one of the main coronary arteries may occur without myocardial infarction. In the latter cases it is presumed that the rate of occlusion is gradual, so that sufficient time is allowed for the development of collaterals. Recently, Wilson and Johnston¹ have again called attention to certain subjective and objective pathologic manifestations in man which they believe are produced by spastic, temporary occlusion of a local division of the coronary arterial tree. They point out the similarity of the electrocardiographic changes in these cases to those which occur experimentally when one of the large coronary arterial branches is temporarily occluded. Inasmuch as these patients always recover, there have been no autopsy observations. The clinical and post-mortem abnormalities produced in man by rapid and high-grade occlusion (without myocardial infarction) of a large coronary branch which is otherwise normal have not, as far as we know, been reported. The case we are presenting is of this variety, and, therefore, is one in which the natural course of events performed an experiment of a rather unusual and fundamental kind. The occlusion was permanent rather than temporary, and therefore myocardial infarction might have been expected to follow. According to our judgment, the heart showed impending infarction. Under these circumstances, the fact that we were able to obtain timely autopsy observations is unique.

CASE REPORT

The patient, a white, male, pencil salesman, aged 52 years, was brought by ambulance and admitted to the Mercy Hospital-Soniat Memorial, New Orleans, Dec. 28, 1940, complaining chiefly of precordial pain, weakness, and shortness of breath. The onset of symptoms occurred suddenly while the patient was seated in a barber's chair, twenty minutes after lunch. Shortly after the onset he made his way to his doctor's office, where he received a brief examination and an injection of morphine. He was then promptly taken to the hospital. The precordial pain was severe and well localized behind the upper half of the sternum. It did not radiate into any of the extremities and was partially relieved by the morphine. The weakness and sweating were marked, and the dyspnea was moderate. Brief nausea and vomiting occurred. Upon reaching the hospital he complained of a severe aching pain over the right eye.

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Hypertension had been present for at least seven years before the onset of the present illness. About three years before the date of admission he had received a transfusion following a hemorrhage from the bowel. Approximately two years earlier he had been hospitalized for two months because of dull, aching pain in the right hypochondriac region. Slight jaundice was present. A diagnosis of gall bladder disease was made, but no operation was performed and recovery was uneventful. With the exception of occasional palpitation, he had experienced no further symptoms previous to the onset of the present illness. There was nothing in the past history to suggest syphilitic or rheumatic infection.

The admission examination showed a well-developed and well-nourished man, supported by two pillows and displaying slight cyanosis and moderate dyspnea. Throbbing of the carotid arteries and slight engorgement of the neck veins were present. The cardiac apex impulse was forceful and well localized in the fifth intercostal space just inside the left midclavicular line. The rhythm was normal. A loud systolic and a moderately loud diastolic murmur were heard at the aortic area. The former was accompanied by a thrill. Similar murmurs had been heard at his doctor's office shortly before admission. However, in spite of repeated previous examinations, he had never been told that he had heart disease. His admission and subsequent blood pressure readings appear in Table I. The right radial pulse was notably smaller than the left. The lungs were normal, and the remainder of the examination was likewise negative.

TABLE I
BLOOD PRESSURE READINGS IN THE ARMS

DATE	RIGHT ARM	LEFT ARM
12/28/40	90/740	140/90
12/30/40	145/100	165/98
1/ 1/41	130/90	144/98
1/ 2/41	124/72	132/78
1/ 4/41	144/90	136/82
1/ 6/41	128/78	122/72
1/ 7/41	145/90	153/82
1/10/41	162/90	134/82

The red, white, and differential blood cell counts were normal. The blood Wassermann reaction was negative. Urinalysis showed a trace of albumin and many hyaline casts. A roentgenogram of the chest, taken with the patient in bed on the third day after admission, suggested enlargement of the heart and the aortic arch. Serial electrocardiograms, one taken on the afternoon of admission and another on the fifth hospitalization day, are shown in Fig. 1.

Commencing with the second day of hospitalization the patient became comfortable. The cyanosis, dyspnea, sweating, and most of the weakness had vanished. Repeated studies of the blood and urine failed to show any additional abnormalities. The icterus index was 10. The temperature varied daily one degree above and below 101° F. until the eighth day, at which time it gradually became normal. The heart appeared to undergo slow, but progressive, dilatation until the time of sudden death on the fourteenth day. The pulse rate averaged 90 per minute. The patient had just extinguished a cigarette and relaxed on the pillow when he was seen to make a few convulsive movements, after which his respiration ceased. Percussion of the chest after death revealed pronounced precordial dullness of wide extent.

Ante-Mortem Diagnosis.—The initial electrocardiogram and the admission blood pressure readings were interpreted by one of us (R. H. B.) to indicate high-grade impairment of blood flow through the right coronary and innominate arteries, respectively. The apparently sudden development of these abnormalities and the aortic insufficiency in a patient who was known to have chronic hypertension led to the im-

mediate diagnosis of dissecting aneurysm. It was further hypothesized that the dissecting column of blood had descended within the aortic wall to the root of the vessel, thus compressing the first segment of the right coronary artery and deforming the aortic valve. The appearance of clinical evidence of either of these events serves to warn of the possibility of fatal hemorrhage into the pericardial sac.² The blood pressure readings that were obtained subsequently from the left arm seemed to indicate that the dissection had reached over the arch to the origin of the left subclavian artery. The severe pain over the right eye might have been additional evidence of impaired flow through the innominate artery. The absence of erythrocytes in the urine and of neurologic symptoms in the lower extremities, together with a persistently normal pulsation in the femoral arteries, suggested that the dissection had not entered the abdominal aorta.

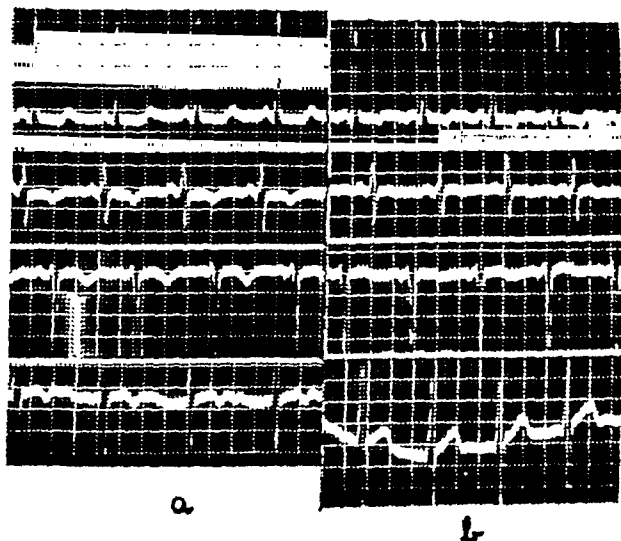


Fig. 1.—*a*, Admission electrocardiogram, Leads I, II, III, and IV F, from above down. *b*, Curve recorded five days after the *a* recording. (See text.)

Autopsy.—The pericardial cavity was greatly distended, and, when opened, emitted a gush of 150 c.c. of blood. The remainder of the large pericardial cavity was filled with a huge, red, soft, ante-mortem clot, and with a heart that was apparently of normal size (actually markedly hypertrophied). The free wall of the left ventricle measured 4 cm. in thickness. The valvular measurements were within normal limits. There was a small atheromatous plaque on the base of the posterior aortic cusp which could not have interfered with valve closure. There were two parallel, circumferentially directed, linear tears in the aortic intima; each measured about 1 cm. in length and was located about 5 cm. above the aortic ring on the anterior wall. The aortic media was split by a dissecting column of blood from the aortic ring to the junction of the arch with the descending portion. In the vicinity of the aortic ring the dissection was limited to the right half of the circumference of the vessel, where it partially surrounded the first segment of the right coronary artery (Fig. 2) and communicated posteriorly with the pericardial cavity through a small hole in the adventitia. A fragment of the clot of the dissecting column of blood may be seen (Fig. 2) compressing the arterial segment from above and from both sides. The cross-section of the vessel was removed from within the aortic wall; it showed the only discoverable (inoffensive?) atheromatous plaque in the coronary tree. In addition, the dissection extended a few centimeters along the innominate, left carotid, and left subclavian arteries. The dissection of the aortic branches involved only part of the circumference of these vessels, and was of such nature as to transform their

lumina into the shape (on cross section) of the new moon. At the extremity of the arch the dissection again communicated with the aortic lumen through a third intimal rupture.

In spite of the apparent closure of the right coronary artery by the dissecting column of blood, the muscle of the ventricles appeared everywhere normal, except for hypertrophy. The intimal surface of the abdominal aorta presented marked atherosclerosis, which, however, did not extend into the main renal arteries. There was a fusiform, aneurysmal dilatation of the left common iliac artery which measured 4 cm. in diameter. The gall bladder was chronically inflamed and a few gallstones were present.



Fig. 2.—Cross section of the right coronary artery as the latter traversed the walls of the aorta and the dissecting column of blood within the aortic media. The dark area above and on either side of the cross section represents a clotted fragment of the dissecting column of blood. The relationship of this clot to the adjacent tissue structure indicates the compression effect it produced upon the coronary arterial lumen. The white patch at 11 o'clock in the vessel wall is an atheromatous plaque. (See text.)

Analysis of the Electrocardiogram.—Inasmuch as the electrocardiographic interpretation was confirmed by the anatomic changes, the manner in which this opinion was reached demands consideration. The opinion was “marked preponderant hypertrophy of the left ventricle, with high-grade impairment of blood flow through the right coronary artery, or impending myocardial infarction.”

In 1934, Wilson, Macleod, Barker, and Johnston³ devised a new method of analyzing the electrocardiogram. Their method consisted of ascertaining the manifest mean electrical axis of QRS and T from the extremity-lead curves by measuring with a planimeter the enlarged areas under the curve of QRS and under the curve of T, respectively. The two axes, thus

obtained, are vector quantities, and, when added (by the parallelogram law), give a new vector which they called the manifest mean electrical axis of QRST, or the ventricular gradient. The three axes are conveniently denoted by \hat{A}_{QRS} , \hat{A}_T , and \hat{A}_{QRST} , respectively.* Theoretical considerations and considerable experimental evidence likewise led them to believe that \hat{A}_{QRS} points in the direction in which the accession process travels over the average element of ventricular muscle; that \hat{A}_T points in the inverse direction, in which the regression process travels over the average element of ventricular muscle; and that \hat{A}_{QRST} points in the direction of a line along which the local variations in the duration of the excited state are greatest. In less technical terms, the ventricular gradient may be said to point approximately in a direction toward regions of the ventricular muscle in which the average onset of regression is relatively early, and away from regions where the average onset is relatively late. We have seen no further comment upon this important study. Since its appearance, one of us (R. H. B.) has had ample occasion to verify the opinion of the authors that [valuable] information, obtainable in no other way, may be derived by this method of analysis. In order to use the method clinically it became necessary to simplify the technique of measurement.⁴ Direct measurements of the electrocardiogram were made by the use of a good hand lens and dividers. Additional error is introduced which reduces the result to an approximation. Nevertheless, as exemplified by the case under discussion, the results have justified the means. In order to make clinical use of the simplified method, it was necessary to obtain some idea of the direction and magnitude of the normal ventricular gradient. A study directed primarily toward this end was undertaken and completed by Bayley, Holoubek, and Baker, in 1940.⁴ They were able to confirm Dr. F. N. Wilson's verbal opinion that the normal ventricular gradient has a base-apex direction. Their study showed that it was possible to predict (almost as a rule) the position of the anatomic axis of the ventricular chambers as a result of the collinear relation which normally exists between the anatomic axis (determined roentgenographically) and the ventricular gradient. During the course of their study upon abnormal subjects it was found, among other things, that the T-wave changes which follow myocardial infarction are best described as the result of a clockwise (negative) rotation of \hat{A}_{QRST} with respect to the base-apex axis in "anterior," and a counter-clockwise (positive) rotation of \hat{A}_{QRST} with respect to the base-apex axis in "posterior," infarction. In serial curves which displayed maximal T-wave changes caused by infarction, they found that \hat{A}_{QRST} often pointed in the direction of a line drawn from the center of the heart toward the right iliac crest in "anterior," and in the direction of a line drawn from the same point toward the left shoulder in "posterior," infarction. They observed further that these rotations or diversions of the

*The arrowhead simply indicates that the quantity is a vector rather than a scalar.

gradient were invariably accompanied by changes in magnitude. They were able to conclude that diversion of the gradient, after infarction, in so far as it is responsible for most of the T-wave change, may be ascribed (as first pointed out by Wilson and co-workers,⁵ and reasserted by Sugarman and associates⁶) to a prolongation of the excited state of the muscle in the immediate neighborhood of the infarcted region. Bayley, Holoubek, and Baker attributed these effects to local ventricular ischemia. A corollary of this assertion is that, after infarction, a reversion of the ventricular gradient following its diversion is caused by disappearance of ischemia from the muscle immediately surrounding the infarct, and is, of course, accompanied by the return of the T waves to a more normal form. Presumably, the disappearance of the local ischemia is the result of establishment in this region of an adequate collateral circulation. For the purpose of the analysis of the electrocardiogram herein presented, the argument may be extended in the following manner.

Let us consider Fig. 3a. The solid zone represents dead, the stippled zone, ischemic, and the clear zone, normal, ventricular muscle. Before infarction, but accompanying coronary occlusion, this same region of the ventricular muscle may be depicted as shown in Fig. 3b. Here, intense ischemia replaces the dead region. It is possible, therefore, that the same kind of T-wave changes which occur after infarction might also occur shortly before. Theoretically, any differences in the typically abnormal form of T which occur immediately before infarction, and become apparent soon (three weeks or more) after it, should be differences in magnitude rather than kind. This statement neglects the effect on the T wave (usually slight) of the QRS changes, which, in turn, result from the absence during systole of forces previously present in the dead region. One of us (R. H. B.) has observed typical "coronary" T waves heralding infarction on more than one occasion when studying serial curves recorded from patients throughout the development of myocardial infarction.

Approximation of the areas under the curve of QRS and under the curve of T in the admission electrocardiogram (Fig. 1) shows that the \hat{A}_{QRS} (Fig. 3c) has undergone an abnormal positive rotation through a polar angle of 70° from the base-apex axis \hat{H} of the ventricular muscle; that the magnitude of \hat{A}_{QRS} is approximately 74.5 millivolt seconds; that \hat{A}_T has undergone a like rotation through a polar angle of 124° from \hat{H} ; that the magnitude of \hat{A}_T is approximately 21 millivolt seconds; and that \hat{A}_{QRST} , having undergone a considerable growth in magnitude, points in the direction of a line drawn from the center of the heart toward the left shoulder. The QRS changes (indicated by \hat{A}_{QRS}) are interpreted as meaning marked preponderant hypertrophy of the left ventricle. The development of this variety of QRS change is often accompanied by a gradual negative (clockwise) rotation and growth of \hat{A}_{QRST} which in-

dicate, we believe, a concurrent development of chronic ischemia of the free wall of the left ventricle. The electrocardiograms which typify these last-mentioned axial changes are currently regarded as representing "relative coronary insufficiency."¹⁷ When the negative rotation of \hat{A}_{QRST} that indicates chronic ischemia of the free wall of the left ventricle is compared with its actual position (Fig. 3c), as derived for the curve under discussion, it is seen that the direction of the latter is simply the inverse of that of the former. This rather unusual occurrence was the result, we believe, of the presence on admission of high-grade ischemia of the

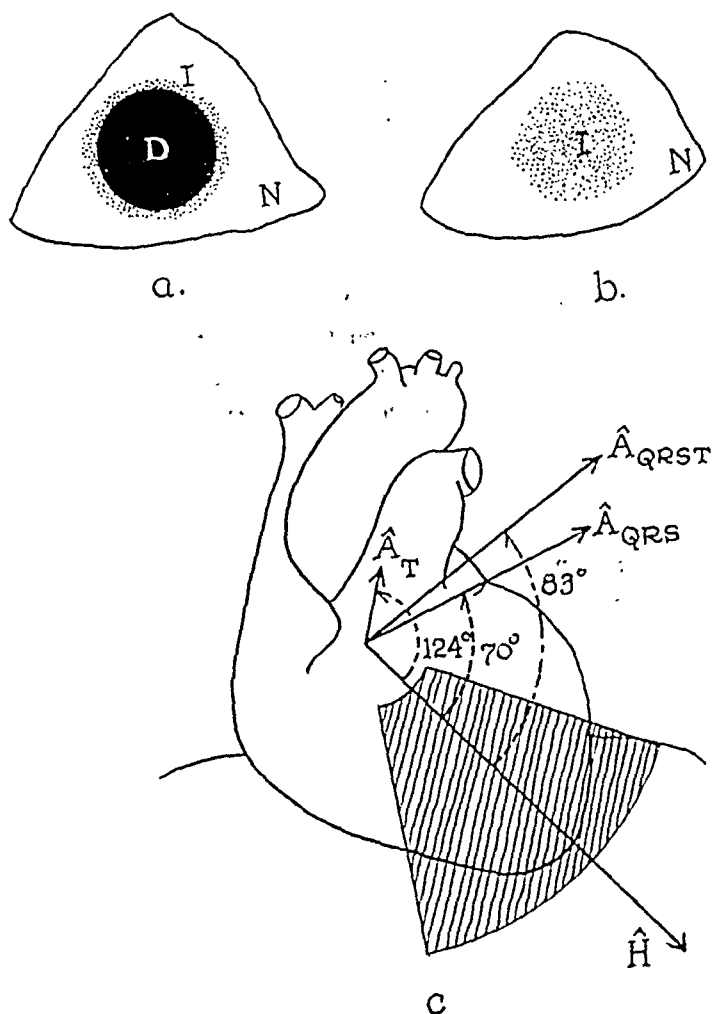


Fig. 3.—a. A diagram of region of ventricular muscle, showing an infarct. *D* indicates dead; *I*, ischemic; and *N*, normal muscle. b. A diagram of the same region of muscle in the proposed state of impending infarction. c. The electrocardiographic axes, \hat{A}_{QRS} , \hat{A}_T , \hat{A}_{QRST} , and the anatomic axis \hat{H} of ventricular chambers. The shaded zone represents the approximate normal region for \hat{A}_{QRS} when \hat{A}_{QRST} and \hat{H} are collinear or in their normal relationship. (See text.)

basal, posterior portion of the interventricular septum and the neighboring diaphragmatic free wall of the left ventricle. In brief, the muscle involved is that ordinarily supplied by the right coronary artery. Moreover, the history of our patient's present illness strongly suggested that the local ischemia was acute rather than chronic. Ante-mortem proof

of the acute character of the ischemia could have been obtained only by a comparison of the curve under consideration with serial curves antedating hospitalization. Unfortunately, no such curves were available.

The second electrocardiogram (Fig. 1), recorded on the fifth day after admission, was analyzed by the same method. The additional T-wave changes in the extremity leads are apparent on inspection. They were the result of partial reversion of $\hat{A}QRST$, and were interpreted as representing diminution in the intensity and extent of the acute local ischemia. The changes in T_4 appear to be confirmatory. Curiously enough, a gradual rise in the blood pressure in the right arm took place concurrently. Both of these local improvements may have been related to some single mechanical factor involving the pressure of the dissecting column of blood. In any event, we believe that lessening of the acute ischemia probably played a major role in delaying the development of a "posterior" myocardial infarct.

The Effects on the Muscle of Acute Local Ventricular Ischemia.—A number of blocks of muscle were removed from various parts of the wall of the left ventricle for the purpose of microscopic study. Routine tissue stains, as well as stains for fat, showed no differences from one region to another. All of the myocardial changes could be ascribed to hypertrophy. The objective effects of acute local myocardial ischemia in man are, as experimental studies suggest, detectable only by the electrocardiogram.

The electrocardiograms herein presented display T-wave changes (caused by gradient rotation) which are etiologically related to those in tracings demonstrated recently by Wilson and Johnston.¹ Their curves were recorded from five patients with angina pectoris, and differ fundamentally from ours by displaying QRS and RS-T junction changes. Additional changes of this kind are related to acute local ventricular ischemia, but are not, strictly speaking, part of it. On this point, we believe, we are in complete agreement with them. They called attention to the independent variation in magnitude and duration of acute local ischemia, on the one hand, and pain (or subjective changes), on the other. We believe that there is a similar and striking correlation in our case. The pain our patient experienced was typical of that which ordinarily occurs with the onset of dissecting aneurysm. As pointed out elsewhere,² it appears to be related to rapid dissection of the aortic wall. Moreover, the pain in our case had vanished by the second day after onset, whereas local ventricular ischemia existed for five days at least (electrocardiographic evidence) or for fourteen days (autopsy evidence). Wilson and Johnston believed that the pain in their cases was of arterial origin (spasm). In our case there was presumably no coronary spasm, but rather a local mechanical compression. We are, therefore, inclined to believe that our patient experienced no pain of cardiac origin. Aside from the evidence which this case adds to theirs, the T-wave changes that

occur immediately before, and persist for a variable, but often long, time after, myocardial infarction are ample evidence that local ventricular ischemia cannot be safely regarded as evidence of the occurrence of cardiac or coronary pain. However, recent opinion has re-emphasized the contrary.⁸

SUMMARY AND CONCLUSIONS

1. A case is presented in which a dissecting aneurysm led immediately to the production of acute local myocardial ischemia by direct compression of the first segment of the right coronary artery. The aneurysm, the local myocardial ischemia, and the nature of its production were diagnosed before death. The autopsy observations are discussed.

2. The diagnosis depended, to a considerable extent, upon the electrocardiographic interpretation. The latter was reached by a method of analysis described in 1934 by Wilson and co-workers²; this method has received little or no comment in the literature, but is one which, on simplification and extension, we believe to be of great clinical usefulness. Using the simplified method, the electrocardiograms herein presented are analyzed.

3. As anticipated, acute local ventricular ischemia of sufficient intensity to produce striking T-wave changes of a kind similar to those that occur in connection with myocardial infarction and last for days or even weeks may be accompanied by no structural changes in the myocardium, and is, more often than not, unassociated directly with cardiac or coronary pain.

We wish to thank Dr. C. F. Bellone for permission to report the case, and Dr. J. R. Schenken and Dr. G. H. Hauser for their kind cooperation in the preparation of the autopsy material.

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3. Wilson, F. N., Macleod, A. G., Barker, P. S., and Johnston, F. D.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, *AM. HEART J.* 10: 46, 1934.
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6. Sugarman, H., Katz, L. N., Sanders, A., Jochim, K.: Observations on the Genesis of Electrical Currents Established by Injury to the Heart, *Am. J. Physiol.* 130: 130, 1940.
7. Graybiel, A., and White, P. D.: *Electrocardiography in Practice*, Philadelphia and London, 1941, W. B. Saunders Co.
8. Blumgart, H. L., Gilligan, D. R., Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries. II. The Production of Myocardial Infarction, *AM. HEART J.* 22: 374, 1941.

Abstracts and Reviews

Selected Abstracts

Harris, A. Sidney, and Moe, Gordon K.: Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration. *Am. J. Physiol.* 136: 318, 1942.*

A method for applying currents controlled as to polarity and rate of flow to the mammalian ventricle is described. Responses from practically the whole ventricular surface were sampled by recording from three local areas simultaneously and changing the positions of the riding contiguous electrode leads from time to time.

Currents, subthreshold for extrasystoles, could give rise to several kinds of changes in the record: 1, "on" and "off" shifts of the base line upon closing and opening the circuit respectively; 2, inflections and changes of level associated with the phases of muscular activity. The amount of displacement of the baseline was reduced during systole, restored to maximal during diastole. After ruling out contact artifacts these features were attributed to conductivity changes associated with contraction and relaxation.

Both anodal and cathodal polarization give rise to oscillating potentials not associated with the phases of the cardiac cycle. The periods of the oscillations were near 40 and 80 msec. Cathodally produced oscillations are higher and are likely to be of the higher frequency (25 cycles per sec., 40 msec. period).

The idioventricular beat threshold was lower for cathodal polarization than for anodal, but the anodal threshold for fibrillation is the lower. The anode is pre-eminently effective in producing fibrillation. With equal applications of currents near fibrillation threshold 96 per cent of all fibrillations were of anodal origin.

Cathodal polarization of suitable intensity usually produces a tachycardia of regularly spaced idioventricular beats, while anodal polarization produces characteristically irregular rhythms. The point of origin of the discharges appears to be more constant in anodal polarization. In all cases of fibrillation resulting from polarizing currents induction is via an accelerating series of discharges from the region of the polarizing electrode.

In the discussion, findings from studies on excitation and spontaneous rhythmicity in nerve and muscle are considered and correlated with the observations on fibrillation. Absence of, or a low rate of accommodation appears to be the condition essential to spontaneous rhythmicity and multiple discharges in response to a single excitation. The probable association of the reduction of accommodation by anodal polarization with the great effectiveness of the anode in the production of fibrillation is pointed out. Direct anodal effects of locally reducing the conduction rate and reducing the refractory period are considered and assigned a contributing role.

AUTHORS.

Graybiel, A.: Diseases of the Heart: A Review of Significant Contributions Made During 1941. *Arch. Int. Med.* 70: 303, 1942.

An annual review and discussion of the literature on cardiology. There is an important section on the heart in wartime with special reference to neurocirculatory asthenia.

McCulloch.

*See Corrigendum, p. 283.

Fedorov, N. A., and Shur, E. I.: The Role of the Viscera in Regulating the Temperature of the Body of an Animal Under Physiologic and Pathologic Conditions. *Am. J. Physiol.* 137: 30, 1942.

Thermogenesis in the viscera (liver and intestines) was studied in normal, artificially cooled and heated animals, as well as during febrile states caused by homogeneous and heterogeneous blood transfusions.

The experiments were made on angiotomized dogs with cannulas in the portal and hepatic veins; in each animal the rectal temperature and the temperature of the blood in the abdominal aorta and the portal and hepatic veins were measured.

The thermoelectric method used throughout the experiments detected changes in temperature with sufficient accuracy and made it possible to study thermotopography in the organism.

In normal fasting dogs the lowest temperature of the blood was found in the aorta and the highest in the hepatic vein.

The experiments have shown important thermogenesis in the intestines.

When the animals were cooled by the application of ice to the skin, the difference in temperature between the blood in the hepatic and the portal veins increased, i.e., there was a rise in hepatic heat production (three to six times the original level), providing the blood flow was accelerated; when the animal was overheated, the reverse took place.

Homogeneous blood transfusion did not bring about noticeable changes in thermogenesis in the liver and the intestines, despite a systemic rise in temperature.

The febrile state caused by heterogeneous transfusion is accompanied by a noticeable increase in thermogenesis in the liver and intestines. A comparative study of the hemodynamic variations has shown that the increase in hepatic and intestinal thermogenesis cannot be explained by the influence of circulatory factors.

After anaphylactic shock, the same changes were observed as in the case of heterogeneous transfusion, but the variations in temperature were much greater, especially with respect to the intestines.

The increase in visceral thermogenesis proceeds parallel to the systemic temperature reaction, i.e., the liver and the intestines participate in determining the febrile process accompanying the transfusion of foreign blood.

The use of the method of E. I. London for studying visceral thermogenesis in angiotomized dogs considerably widens the sphere of its application and promises to give results of great practical and theoretic interest.

AUTHORS.

Hsu, S-H, Hwang, K., and Chu, H-N.: A Study of the Cardiovascular Changes Induced by Stimulation of the Motor Cortex in Dogs. *Am. J. Physiol.* 137: 468, 1942.

By stimulation of the motor focal points on the sigmoid gyrus of the dog anesthetized with chloralose, there is always a fall of blood pressure. The depressor effect thus produced is always associated with the muscular movement in non-curarized animals, but the production of the former is not dependent on the latter.

The intensity of the depressor effect evoked from the cortical stimulation in dogs is determined by the strength of the stimulating current and by the particular motor focal point that is stimulated.

The heart rate is usually increased about 20 per cent on stimulation of the motor area in dogs, but the change of the heart rate is not a casual factor in the depressor effect, since the latter is not influenced or abolished by section of both vagi.

The respiratory movements are usually decreased in amplitude and increased in number, and occasionally apnea may occur during cortical stimulation.

The renal volume is always increased accompanying the fall of blood pressure following cortical stimulation. Vasodilation of the visceral organs is probably the cause of the depressor effect.

AUTHORS.

Master, A. M., Striker, J., Grishman, A., and Dack, S.: Effect of Undernutrition on Cardiac Output and Cardiac Work in Overweight Subjects. *Arch. Int. Med.* 69: 1010, 1942.

The effect of reduction in weight on the oxygen consumption, pulse rate, blood pressure, cardiac output and cardiac work was studied in five normal overweight subjects who were placed on a 1,200 calorie diet. The modified Grollman acetylene method and the Wetzler-Boeger physical method were used to determine the cardiac output. Loss of weight was accompanied by an average drop of 16 per cent in oxygen consumption, an average increase of 24 per cent in the arteriovenous oxygen difference, and an average drop of 30 per cent in the cardiac output. These changes were accompanied by slowing of the pulse rate and slight lowering of the blood pressure. Since cardiac work is a function of cardiac output and mean arterial pressure, it was calculated that the low caloric intake and the reduction in weight resulted in a distinct diminution in the work of the heart (average, 35 per cent). This is of great benefit to overweight persons, in whom the cardiac work is increased, and is of particular importance in the treatment of patients with heart disease, whose cardiac reserve is diminished and who are barely able to compensate for any additional strain.

AUTHORS.

Sigler, L. H.: The Hyperactive Cardioinhibitory Carotid-Sinus Reflex as an Aid in the Diagnosis of Coronary Disease: Its Value Compared With That of the Electrocardiogram. *New England J. M.* 226: 46, 1942.

A comparative study is presented of the incidence of a hyperactive cardioinhibitory carotid-sinus reflex and of electrocardiographic abnormalities in a series of 1073 cases, largely ambulatory, of coronary disease. It was found that 91.3 per cent of the men and 72.6 per cent of the women in this series showed the cardioinhibitory response, whereas only 63 per cent of the men and 71.9 per cent of the women showed abnormalities in the electrocardiogram. High degrees of cardioinhibitory response, which are definitely abnormal, occurred in 61.8 per cent of the males and 42.9 per cent of the females. Marked electrocardiographic abnormalities occurred in only 37.4 per cent of the males and in 40 per cent of the females.

It is believed that the hyperactive cardioinhibitory carotid-sinus reflex may be used as an aid in the diagnosis of coronary disease in persons of the coronary age who present suspicious complaints. As such, it is often of greater value than the electrocardiogram and will suggest the correctness of the diagnosis when the electrocardiogram may be entirely misleading.

The explanation for the frequency of the hyperactive reflex in coronary disease is at the present state of knowledge purely theoretical. It may be due to local ischemia in the heart, which lowers the resistance in the vagal ganglions and in the myoneural junctions, or which produces some chemical changes that sensitize the vagus nerves locally.

AUTHORS.

Langendorf, R., and Kovitz, B.: Acute Myocardial Infarction Without Deviation of the S-T Segment in the Electrocardiogram. *Am. J. M. Sc.* 204: 239, 1942.

A case is reported with recent myocardial infarction, proven at autopsy, in which elevation of the S-T segment was absent in the electrocardiogram taken during the acute stage. The absence of involvement of the subepicardial myocardium over the infarcted area is considered as the possible cause for the atypical record.

Cases of recent myocardial infarction with delayed electrocardiographic signs also may represent such cases of infarction of the subendocardial layers without involvement of the subepicardial layers of the myocardium.

Other causes for absence of this electrocardiographic sign must be excluded before this interpretation is entertained.

AUTHOR.

Robb, R. C., and Robb, J. S.: **Experimental Bundle Branch Block After Ablation of One or Both Ventricles.** *Am. J. M. Sc.* 204: 313, 1942.

In order to record a QRS-T complex, the presence of the "free" (i.e., nonseptal) walls of either (or both) right or left ventricles is unnecessary.

Not even the right side of the septum depends entirely for its excitation on conduction pathways which first reach the papillary muscles at the apices and then turn back. It contracts with a normal S-A rhythm when such pathways are interrupted by the total ablation of the "free" portions of both right and left ventricles, i.e., impulses are conducted from the main branches directly to the septum.

These experiments have not proven definitely whether the electrocardiograms recorded from the isolated septum are due to excitation of the septal muscle alone or whether action currents passing in the right and left branches (whose peripheral expansions were amputated) also produce some effect.

Not only does electrical activity of the free wall of each ventricle affect the electrocardiogram, but various portions of each wall have a characteristic effect.

These experiments do not support the theory that an electrocardiogram is summation of only one dextro- and one levocardigram.

That the amplitude of deflections increases when the contact surface of the heart diminishes suggests that normally there is considerable neutralization of current.

So-called "axis deviation" appears when less rather than more of a given ventricle is present. Hence it appears to be due to loss of electrical components, with consequent change in the algebraic sum.

Laboratory animals, dogs, cats and rabbits, conform to the newer or American terminology for bundle branch block; i.e., when the right side of the heart is anatomically and functionally absent, there is a deep wide S_1 and a tall wide QRS_2 . The reverse is true for anatomic and functional absence of the whole left ventricle.

AUTHORS.

Sabathié, L. G., Gaspary, F., and Voogd, M.: **Complete Auriculoventricular Block and Auscultable Auricular Flutter With Phonocardiographic Registration.** *Rev. argent. de cardiol.* 9: 51, 1942.

A case of auscultable auricular flutter and auriculoventricular block with auricular flutter is presented in which the diagnosis was made clinically.

The frequency of this combination, its clinical diagnosis and the probable origin of the auricular sounds in flutter are discussed.

AUTHORS.

Danielius, G.: **Absence of the Hilar Shadow. A Diagnostic Sign in Rare Congenital Cardiac Malformations (Truncus Arteriosus Solitarius With Heterotopic Pulmonary Blood Supply).** *Am. J. Roentgenol.* 47: 870, 1942.

A case of right-sided truncus aorticus solitarius with heterotopic pulmonary blood supply is analyzed anatomically and roentgenographically. The absence of the hilar shadow in the roentgenogram is explained through the absence or the marked underdevelopment of the right and left pulmonary artery. The pulmonary circulation in these cases is maintained through the patent distal part of Botallo's duct, through supernumerary bronchial arteries or through a branch of a subclavian artery. The roentgen diagnosis of this condition can be made when absence of the hilar shadows is associated with a deep depression at the site of the pulmonary conus.

WILLIAMS.

Goldburgh, H. L., Baer, S., and Lieber, M. M.: *Acute Bacterial Endocarditis of the Tricuspid Valve.* *Am. J. M. Sc.* 204: 319, 1942.

The relative incidence of acute bacterial endocarditis of the tricuspid valve was considered. In 26,007 necropsies, 646 cases of acute bacterial endocarditis occurred. The mitral valve alone was involved in 47.6 per cent cases, the aortic valve alone in 25.4 per cent, and the tricuspid alone in 3.1 per cent. Involvement of the right side of the heart whether alone or in combination with other valve lesions, was found in 8.2 per cent cases.

Twenty cases in which the endocarditis was restricted to the tricuspid valve were studied. Of these 20 cases, nine were due to the pneumococcus. The pneumococcus is more apt to produce right-sided acute bacterial endocarditis, for nine (14.5 per cent) of 62 cases of pneumococcal endocarditis were restricted to the tricuspid valve as contrasted to the 3 per cent of 646 cases mentioned above.

Emphasis is placed upon the lack of diagnostic auscultatory findings in acute tricuspid bacterial endocarditis. In but eight of the twenty cases was mention made of any murmur being heard, and in none of these was the murmur found over the tricuspid area.

AUTHORS.

Galvin, L. F.: *The Virginia Program for Children With Rheumatic Fever.* *The Child* 6: 164, 1942.

The author describes briefly the activities of the Children's Bureau through Federal aid for cardiac children as a part of the application of the Crippled Children's Act. The state program in Virginia is well organized and may serve as an example to other states.

MCCULLOCH.

Rakov, H. L., and Taylor, J. S.: *Acute Disseminated Lupus Erythematosus, Without Cutaneous Manifestations and With Heretofore Undescribed Pulmonary Lesions.* *Arch. Int. Med.* 70: 88, 1942.

A consideration of the complex clinical manifestations of lupus erythematosus disseminatus is combined with the report of a case in which the patient exhibited pronounced pulmonary signs and lesions but showed no cutaneous eruptions at any time.

AUTHORS.

Schroeder, H. A.: *Studies on "Essential" Hypertension. IV. Early Arterial Hypertension.* *Am. J. M. Sc.* 204: 62, 1942.

Fifty patients exhibiting slight elevation of the blood pressure were studied with a view to ascertaining the varieties of clinical disturbance. Thirty-seven were found to be suffering from various diseases of the kidneys, and 11 others from dysfunctions of the nervous system. In addition, every patient exhibited nervous tension of some degree. In a few cases the onset of hypertension was associated with a definite physical or psychologic disturbance. It is probable in the light of this experience that arterial hypertension is the result of a number of factors, differing in different individuals.

AUTHOR.

Markham, J. D., and Bloom, N.: *The Significance of Electrocardiographic Changes in Malignant Hypertension.* *J. Lab. & Clin. Med.* 27: 1156, 1942.

In evaluating the significance of the electrocardiographic changes in malignant hypertension, a tabulation was made of the age at which each patient died. The greatest mortality was in the group 35 to 39 years old. The majority of deaths

occurred after the third decade was reached, while none occurred over 50 years of age. This indicates that the electrocardiogram is a reliable guide in following the progress of malignant hypertension and has some prognostic value. Senile degenerative changes, which may modify its usefulness, have not appeared. It is evident that the characteristic changes observed in this series are due solely to the effect of malignant hypertension on the heart.

AUTHORS.

Thomas, C. B.: Experimental Hypertension From Section of Moderator Nerves: Relationship to Presence of Kidney Tissue. *Proc. Soc. Exper. Biol. & Med.* 48: 24, 1941.

The author attempted to establish by means of acute experiments whether antitoxin plays a role in the hypertension resulting from moderator nerve section. The results indicate that removal of both kidneys does not prevent the immediate appearance of a pressor response to moderator nerve section. It would seem that circulating pressor substances arising from the kidney are not demonstrably important in the production of acute neurogenic hypertension.

KERSHBAUM.

Megibow, R. S., Katz, L. N., and Rodbard, S.: The Mechanism of Arterial Hypertension in Experimental Hydronephrosis. *Am. J. M. Sc.* 204: 340, 1942.

Complete unilateral ureteral occlusion in uninephrectomized dogs and complete bilateral ureteral occlusion are followed by a rise in the systemic arterial blood pressure which persists until the animals die of uremia.

Partial bilateral and complete or partial unilateral ureteral occlusion are followed by a transient elevation of the arterial blood pressure.

The addition of unilateral hydronephrosis to contralateral renal ischemia intensifies any tendency to hypertension. This indicates that the hydronephrotic kidney is actively concerned in the genesis and maintenance of arterial hypertension.

Evidence is presented that this mechanism is twofold, in that ischemia and destruction of normal renal tissue probably proceed simultaneously in the same kidney, the initiating factor being a rise in ureteral and intratubular pressure.

An explanation is offered for the occasional occurrence of normotension and renal excretory insufficiency observed in hydronephrosis.

AUTHORS.

Foà, P. P., Foà, N. L., and Peet, M. M.: Effect of Pregnancy on Experimental Renal Hypertension in Rats. *Am. J. M. Sc.* 204: 350, 1942.

The normal systolic blood pressure of the young adult albino rat was found to average 85 mm. Hg (60 to 130). It is slightly lower during the summer.

Ether anesthesia has no appreciable effect on the systolic blood pressure of normal rats.

Systolic blood pressure in rats does not change significantly during normal pregnancy.

Hypertension of several months' duration can be produced in rats by constricting one renal artery without damage to the general health of the animal.

The systolic blood pressure of rats with hypertension due to the constriction of one renal artery is sharply reduced during pregnancy from an average maximum of 174 to an average minimum of 103 mm. Hg.

After delivery the systolic blood pressure again rises to hypertensive levels, reaching an average of 180 mm. Hg.

Constriction of the renal artery of pregnant rats is followed by rapid decline and death. Hypertension may or may not occur.

The influence of pregnancy on experimental renal hypertension in rats is discussed. It is suggested that the drop in blood pressure might be due to an endocrine mechanism.

AUTHORS.

Saxton, J. A., Jr.: Elastic Properties of the Rabbit Aorta in Relation to Age. Arch. Path. 34: 262, 1942.

A study has been made of the elastic properties and morphologic character of the rabbit aorta at different ages (6 months to 5 years) and at three levels (upper, middle and lower regions of the descending thoracic portion). Segments (rings) of aorta, cut 5 mm. in length, from the three levels were subjected to increasing loads up to 180 Gm., and changes in their circumferences with and without loads were measured. From these measurements ratios of extension to original circumference, retraction to extended circumference and increase in circumference after unloading to original circumference were calculated. These ratios were compared graphically and as values of moduli at corresponding stresses in relation to age and to the level from which the segments were taken.

With advance in age the rabbit aorta becomes more extensible, shown by increasing values of the ratio of extension to original circumference and by decreasing values of Young's modulus at corresponding loads.

At the maximum load used the ratio of extension to original circumference was 124 per cent at 6 months and 152 per cent at 5 years.

No change in the capacity to retract after extension, expressed as the ratio of retraction to extended circumference, was observed in relation to age. At the maximum load used this ratio varied between 50 and 55 per cent.

With advance in age the rabbit aorta becomes less able to return to its original circumference after stretching, evidenced by increasing values of the ratio of increase in circumference after unloading the maximum load to original circumference (from 6 per cent at 6 months to 24 per cent at 5 years) and by decreasing values of the modulus for this relation at corresponding loads.

With advance in age the smooth muscle of the media is gradually replaced by collagenous tissue and there is an increase in fine elastic fibrils between the elastic membranes. The aortas of old rabbits, judged by measurements and by the waviness of the elastic membranes, appear slightly contracted in their post-mortem state as compared with aortas of young rabbits, and these differences may be associated with differences in the elastic properties.

The upper portions of the aorta were capable of more extension and retraction than the lower portions under comparable conditions.

The observed changes in elastic properties suggest that the rabbit aorta, in contrast to the human aorta, does not age so rapidly as compared with other organs and is still a relatively young structure at the end of the life span.

AUTHOR.

Chapman, E. M., and Asmussen, E.: On the Occurrence of Dyspnea, Dizziness, and Precordial Distress Occasioned by the Pooling of Blood in Varicose Veins. J. Clin. Investigation 21: 393, 1942.

The authors believe that undue fatigue, shortness of breath, dizziness, fainting, and precordial distress may be occasioned by pooling of blood in varicose veins. These clinical investigations offer evidence that the circulatory efficiency is decreased by such extensive pooling and that removal of this peripheral blood reservoir restores the hemodynamics of the subjects toward normal and relieves their symptoms.

AUTHORS.

Wolf-Heidegger, G.: Concerning the Finding of Valves in the Veins of the Small Intestine. *Cardiologia* 5: 359, 1941.

Valves were able to be demonstrated in the veins of the small intestine of various small mammals (dog, cat, rabbit, rat, mouse).

Of the kinds of animal examined, the dog and the cat possess the most and largest vein valves. Age differences were not observed.

Vein valves are present in the first extraintestinal portion of the mesenteric veins in the immediate vicinity of the mesenteric border, in the large veins perforating the muscular layers and in the vein system of the lamina intermuscularis.

The importance of these valves is discussed.

AUTHOR.

Hertzman, A. B., and Roth, L. W.: The Absence of Vasoconstrictor Reflexes in the Forehead Circulation. Effects of Cold. *Am. J. Physiol.* 136: 692, 1942.

The absence of vasoconstrictor reflexes in the forehead is demonstrated by the following evidence:

The spontaneous rhythmic constrictions of vasomotor origin in the finger of the resting subject are absent from the forehead.

The vasoconstrictor reflexes elicited by startle, awakening, a deep breath, immersion of the hand in ice water or local cold to the forehead are wholly absent in the latter.

The vascular reactions of the forehead skin to local cold are like those of a sympathectomized digit. Constriction is gradual as the temperature of the skin falls and seems to be due to the direct effects of cold on the vessels.

The reactive dilatation to cold which occurs in the fingers, was not observed in the forehead skin.

Occasionally, there was indication of a vasodilator reflex in the forehead skin at the time of a powerful constriction in the finger.

AUTHORS.

Gregg, D. E., Shipley, R. E., Eckstein, R. W., Rotta, A., and Wearn, J. T.: Measurement of Mean Blood Flow in Arteries and Veins by Means of the Rotameter. *Proc. Soc. Exper. Biol. & Med.* 49: 267, 1942.

The rotameter has been adapted to the measurement of mean blood flows in arteries and veins and also in cardiac input. A description of the apparatus is given and the proper methods of its use, sources of error and procedures for calibration are discussed. Typical records are shown. Tests indicate that in routine use the instrument will measure blood flow with an error of less than 10 per cent. An advantage over other methods of measuring blood flow is that the experimenter can determine at a glance the moment to moment flow during the time that flow is actually being measured.

WILLIAMS.

Davis, H. A., and Eaton, A. G.: Comparative Effects of Horse Serum, Horse Serum Albumin and Horse Serum Globulin in Experimental Shock. *Proc. Soc. Exper. Biol. & Med.* 49: 359, 1942.

The experiments were conducted on dogs under light ether anesthesia. Shock was produced by graded hemorrhage from the carotid artery. The sera were administered by gravity, through a cannula inserted into the right femoral vein, in amounts equal to the quantity of blood removed. The administration of whole serum caused a rise in blood pressure which was maintained and the animals recovered. Mild dyspnea was observed for a short time following the injection. The administration of serum globulin caused marked dyspnea. The three dogs

which survived showed moderate rise in blood pressure following the injection but were sick and listless for several days. The fourth dog died twelve hours after the injection and autopsy revealed subcutaneous, subserosal, subpleural, subepicardial and subendocardial hemorrhages, a congested liver and a contracted spleen. The administration of serum albumin resulted in a rise of blood pressure to almost the initial level which was maintained, and all of the animals recovered without after-effects. Horse serum albumin and serum globulin affect dogs in a manner similar to bovine serum albumin and serum globulin, while horse serum is less toxic than bovine serum. It is suggested that some substance in whole horse serum, possibly serum albumin, tends to diminish the toxicity of the globulin.

WILLIAMS.

De Gowin, E. L., Harris, J. E., and Bell, J.: Rates of Hemolysis in Human Blood Stored in Dextrose Solutions and in Other Mixtures. *Proc. Soc. Exper. Biol. & Med.* 49: 481, 1942.

Hemolysis during storage at 2° C. is markedly inhibited by the addition of dextrose to blood-citrate mixtures. Maximal inhibition of hemolysis is obtained with a final concentration of dextrose of approximately 2 per cent and this mixture permits the safe storage of blood for about thirty days. Sucrose is not so effective as dextrose, and NaCl and KCl increase the rate of hemolysis.

WILLIAMS.

Leinoff, H. D.: Acute Coronary Thrombosis in Industry: I. Direct Nonpenetrating Injuries, With Report of Cases. *Arch. Int. Med.* 70: 33, 1942.

Direct nonpenetrating injury of the chest can produce nonfatal disabling heart damage.

The resulting disability is due to a combination of structural and functional changes.

The clinical picture is that of an acute pathologic condition of the heart and closely resembles that of coronary occlusion, from which it is differentiated by the history.

The history is the most important single factor in determining causal relation and the subsequent degree of disability.

The electrocardiographic studies are important and usually show changes associated with acute lesions.

This clinical syndrome should be considered in the presence of any injury of the chest.

AUTHOR.

Scherf, D., and McGavack, T. H.: The Estrogen-Like Action of Desoxycorticosterone Acetate Upon the Altered Electrocardiogram Seen in Various Hypo-Ovarian States. *Am. J. M. Sc.* 204: 41, 1942.

Six women with clinical manifestations of hypo-ovarianism and electrocardiographic changes, typical of such a state, have been described.

The influence of desoxycorticosterone acetate and ovarian follicular hormone on the clinical and electrocardiographic disturbances present in each 4 of these has been recorded and evaluated. In 2 additional individuals, changes following the administration of desoxycorticosterone acetate have been noted.

In each of the 4 patients to whom administered, estrogens returned the previously altered electrocardiogram to normal. Total dosages necessary for this effect varied from 14,000 to 50,000 international units.

In all 6 patients, the previously altered electrocardiogram reverted to normal under the influence of desoxycorticosterone acetate in total doses of 30 mg. to 60 mg. The response was equivalent in kind and in degree to that observed following the ad-

ministration of ovarian follicular hormone, provided proper dosages were employed.

Possible explanations of this action of desoxycorticosterone acetate upon the heart are discussed. Among these must be included a direct action by way of blood vessels and blood and tissue electrolytes, and an indirect action by way of other endocrine glands, notably the pituitary and the gonads.

AUTHORS.

Ziskin, T., and Dumas, A. G.: Observations on the Electrocardiogram in Epilepsy and Comparison With Electrocardiogram in Seizures Following Convulsant Drug Therapy. *J. Lab. & Clin. Med.* 27: 1249, 1942.

The electrocardiographic findings which the authors observed during and after epileptic seizures tend to show that cardiovascular changes occur following epileptic seizures, and that these changes are part of circulatory changes throughout the body. As a result of this, and from the experimental and clinical observations of other workers, the supposition is made that the epileptic seizures are due to a cerebral anoxemia resulting from an ischemia of the brain following vasoconstriction. This is probably the result of an electrochemical change and adrenalin-like action on the cerebral vessels.

After comparing their findings with those of other workers who studied the electrocardiographic changes following seizures after convulsant drug therapy, they conclude that the physiologic changes during and after convulsive seizures from excitant drugs are the same as those due to epilepsy; also that the extrinsic factors, such as insulin shock and metrazol, probably produce a similar adrenalin-like reaction as the intrinsic factor which brings on the cerebral ischemia and anoxemia in epileptic seizures.

AUTHORS.

Fletcher, P. H., and Schroeder, H. A.: Studies on Congestive Heart Failure. II. Impaired Renal Excretion of Sodium Chloride. *Am. J. M. Sc.* 204: 52, 1942.

In 4 patients convalescent from severe congestive heart failure there was found an impairment of the ability of the kidney to excrete sodium and chloride (as compared to 2 subjects without heart disease), when the concentration of these ions in the serum was experimentally elevated above normal.

Mercurial diuretics increased the excretion of sodium and chloride by these same subjects.

AUTHORS.

Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D.: The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram, With Particular Reference to T Wave Changes. *J. Clin. Investigation* 21: 409, 1942.

Exercise lowers the T waves of the normal human electrocardiogram, with return toward normal in less than a minute. During recovery the amplitude of T may be greater than normal.

Adrenalin lowers the T waves. The effect lasts from fifteen to thirty minutes.

Ergotamine tartrate raises the T waves. This effect lasts as long as an hour.

Atropine lowers the T waves. The effect is maximal in one hour but may last ninety minutes.

Mecholyl lowers the T waves and causes tachycardia without preliminary bradycardia.

Right carotid sinus pressure causes an elevation of the T waves.

The importance of taking these changes into account when interpreting electrocardiograms is stressed.

AUTHORS.

Decherd, G. M., Jr., and Hermann, G. R.: *The Results of Treatment of Various Cardiac Mechanism Disturbances.* Texas State J. Med. 37: 767, 1942.

In 116 cases of this series, atrial or auricular fibrillation was present, 73 times in patients with hypertensive heart disease, 20 times in rheumatics, 15 times in syphilitics, 5 times in thyrotoxicos, 1 was due to over-digitalization, and 3 were of unknown etiology. Only two cases were refractory to digitalis, and one of these seemingly became responsive after calcium administration. Quinidine sulphate restored normal sinus mechanism in 12 out of the 16 cases in which it was used.

Atrial flutter was studied in 25 cases, most of which were of hypertensive and arteriosclerotic heart disease. Digitalis was administered to produce fibrillation in 17 cases, and in 9 of these subsequent cinchonization was necessary to restore the normal sinus rhythm. Quinidine alone was successful in 9 out of 12 cases.

Paroxysmal atrial tachycardia was recorded in 27 hospital cases, 14 of whom had died of heart disease at the time of the summarization. Carotid sinus stimulation was effective in stopping the attack in 5 out of 8 cases; quinidine in 5 out of 6 cases; intravenous digitalis in 3 out of 5 cases; prostigmin in 1 out of 3 cases; morphine in 2 out of 2 cases.

Paroxysmal ventricular tachycardia was most serious; 7 of 8 cases had died; 3 out of 5 cases responded to quinidine. Adams-Stokes seizures were temporarily controlled in some cases by barium chloride, ephedrine, adrenalin in oil, thyroid extract and paredrine hydrobromide. Carotid sinus attacks were prevented by the use of belladonna or atropine.

AUTHORS.

Chen, K. K., Bliss, C. I., and Robbins, E. B.: *The Digitalis-Like Principles of Calotropis Compared With Other Cardiac Substances.* J. Pharmacol. & Exper. Therap. 74: 223, 1942.

Of the three digitalis-like principles of Calotropis, their potencies relative to each other and to ouabain were in the following order when tested in parallel:

Drugs in Anhydrous Form	In Frogs	In Cats
Ouabain	144	121
Calotropin	100	100
Calotoxin	76	92
Uscharin	42	69

All differences were significant except that between calotropin and calotoxin in cats.

By simultaneous comparison of the above 4 drugs with 8 other cardiac principles in etherized cats, their potencies in anhydrous form relative to ouabain were convallo-toxin 112, ouabain 100, β -antiarin 90, α -antiarin 87, cymarin 86, calotropin 83, coumagine HCl 78, calotoxin 76, emicymarin 63, bufotalin 61, uscharin 58, and periploeymarin 55. Differences between pairs in the above series that are less than 18 per cent of the smaller potency cannot be considered significant.

For 10 of the above drugs, the median lethal dose had also been determined individually over a period of several years and in four cases the new values differed significantly from the earlier determinations, demonstrating the importance of parallel tests with group standards in experiments on the toxicity of cardiac substances to cats.

The lethal dose in cats showed a closer relation to the size of the heart, in terms of the two-thirds power of its fresh weight, than to the weight of the body, so that comparisons of drugs corrected for size of heart were the more precise and have been quoted in the summary. Due to the high correlation between heart weight and body weight, relative potencies determined by both procedures agreed within a small percentage.

AUTHORS.

Chen, K. K., Steldt, F. A., Fried, J., and Elderfield, R. C.: The Action of Simple Lactones Related to Cardiac Aglycones. *J. Pharmacol. & Exper. Therap.* 74: 381, 1942.

Twenty-seven unsaturated lactones related to cardiac aglycones have been studied pharmacologically.

β , γ -Angelica lactone, the lactone of 21-hydroxy- $\Delta^{20,22}$ -norcholeonic acid, methyl coumalate, and ethyl coumalate, cause systolic standstill of frogs' ventricles when adequate doses are injected into the ventral lymph sac. β -(β -Naphthyl)- $\Delta\alpha$, β -butenolide has a suggestive action.

In cats, β , γ -angelica lactone and methyl and ethyl coumalates all produce a fall of blood pressure and fail to induce emesis. Electrocardiographically, no ectopic rhythm, multiple foci of impulse formation, various forms of aberrant QRS complexes, and terminal ventricular fibrillation occur as the lethal dose is slowly approached. The evidence in cats is therefore not indicative of any digitalis-like action of the three substances.

AUTHORS.

Obreshkove, V.: Cardiac Inhibition of a Cladoceran and the Action of Acetylcholine and Physostigmine. *Proc. Soc. Exper. Biol. & Med.* 49: 427, 1942.

The heart of *Daphnia magna* can be arrested by applying a mechanical stimulus to a region in the digestive tube where the stomach enters the intestine. The period of heart arrest varied from about 2.5 to 21 minutes. For several minutes after escape from inhibition the heart showed grouped beats which were feeble in character, irregular in amplitude and much slower than normal. Within less than 20 seconds after the addition of acetylcholine there was observed a sudden increase in the frequency of the heart beat, in some instances it was equal to or greater than the normal rate, and the cardiac activity became immediately more powerful and regularly rhythmic in character. If the animals were treated with physostigmine for a period of from 5 to 15 minutes before the cardiac inhibition was produced, the cardiac rhythm became regular and there was re-establishment of the normal rate of heart beat almost immediately after escape from inhibition.

WILLIAMS.

Martin, G. J., and Hueper, W. C.: Biochemical Studies of Atheromatous Animals. *Proc. Soc. Exper. Biol. & Med.* 49: 452, 1942.

Following the oral administration of cholesterol to rabbits or the parenteral administration of polyvinyl alcohol to dogs it was found that there was a decrease in the speed of oxygenation of the red cells. It is suggested that this effect is due to a coating action of the macromolecular compounds used. Plasma volumes increased approximately 100 per cent during the first twenty-four hours following injection of 50 c.c. of 5 per cent solution of polyvinyl alcohol. This osmotic activity is probably due to the slowness with which the colloid is removed from the blood and to its coating the intima with a film which may interfere with the escape of water from the liquid component of the blood.

WILLIAMS.

Jacobson, S. D., and Smyth, C. J.: Plasma Volume Changes Following the Intravenous Injection of Pectin and Physiologic Saline in Man. *Proc. Soc. Exper. Biol. & Med.* 50: 218, 1942.

The subjects for the experiments were 9 male patients who were normal with respect to the cardiovascular system. An average of 690 c.c. of 0.75 per cent pectin solution were injected intravenously in each of 5 patients at the rate of

10 c.c. per minute. 1000 c.c. of saline were injected intravenously in each of 4 patients. Plasma volume determinations were made before injection, at the end of infusion on 2 patients receiving each solution, 4 hours after the end of infusion on the other 5 patients, and 24 hours after the end of infusion on all patients. Immediately following the injection of pectin the plasma volume was increased by an amount equal to the volume of solution injected, 4 hours later the increase in volume was greater than that of the injected solution, and at the end of 24 hours there was an increased plasma volume in 3 patients. Immediately following the injection of saline solution the increase in plasma volume was considerably less than the volume of injected solution and was still less at the end of 4 hours, and the plasma volume had returned nearly to normal at the end of 24 hours.

WILLIAMS.

Rath, M., and Krantz, J. C., Jr.: Nitrites. X. Effect of Sodium Nitrite Upon the Blood Pressure of Unanesthetized Hypertensive Rats. *Proc. Soc. Exper. Biol. & Med.* 50: 248, 1942.

Systolic blood pressures in the tails of rats were determined by a plethysmographic method. Rats were rendered hypertensive by (a) subtotal nephrectomy or (b) bilateral wrapping of cellophane on the kidneys or (c) unilateral nephrectomy combined with unilateral cellophane wrapping. An oral dose of 4 mg. of sodium nitrite per 100 Gm. of body weight caused the blood pressure to drop from an average of 140 mm. to an average of 118 mm. in thirty minutes. Intraperitoneal injection of 2.5 mg. of sodium nitrite per 100 Gm. of body weight caused the blood pressure to drop from an average of 140 mm. to an average of 116 mm. in twenty minutes.

WILLIAMS.

Hirschfelder, A. D., and Tamoales, G.: Inhibition of Experimental Auricular Fibrillation by Procaine and Other Substances. *Proc. Soc. Exper. Biol. & Med.* 50: 272, 1942.

Auricular fibrillation in anesthetized dogs was produced either by faradic stimulation of the right auricle or by dropping acetyl beta methyl choline chloride solution onto the wall of the atrium. Ten to 20 mg. per kilo of procaine intravenously stopped fibrillation, produced by minimal effective faradic stimulation, for about five minutes. Forty to 80 mg. per kilo prevented fibrillation from maximal faradic stimulation. One to 6 mg. per kilo of procaine stopped fibrillation from being induced by acetyl beta methyl choline chloride solution within thirty-five seconds, the smaller doses of procaine being effective only for about five minutes. Similar effects in inhibiting auricular fibrillation were obtained with p-butyl amino-benzoyl-dimethyl amino-ethanol hydrochloride and with 2-butyloxyquinoline carboxylic acid-4-diethylethylene diamide hydrochloride.

WILLIAMS.

Corrigendum

The abstract, "Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration," by Harris and Moe, page 271 of this number is a correction of an abstract of the same title appearing in the October number of this Journal, page 577.

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*Executive Committee.

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Original Communications

WILLIAM WITHERING—A BICENTENARY TRIBUTE

GUSTAV NYLIN, M.D.

STOCKHOLM, SWEDEN

AS A YOUNG, 23-year-old student at Edinburgh University, Withering wrote in a letter to his parents, in 1764, that the teacher of botany annually awarded a gold medal to encourage the best among his pupils. This led to great competition among the young men, "though," continues Withering, "I confess, it will hardly have charm enough to banish the disagreeable ideas I have formed of the study of botany." And yet, remarkably enough, it was as a botanist that he was to become famous and honored, and it was in the capacity of both doctor and botanist that he was to write his famous paper on the medical use of digitalis.

Withering was born March 28, 1741, at Wellington, in the Midlands. His father was a respected and much-sought-after doctor, and his mother came of an old, well-known medical family. They had three children. Withering's school career and upbringing were in no way remarkable. He learned the elements of the classics, mathematics, geography, and history, from a clergyman in the neighborhood. He did not distinguish himself in any respect either during this period or during his earlier years at the University. It was his father's wish that his son should become a doctor, and this was in conformity with Withering's own plans for his future.

At the age of 21 he began to study at the University of Edinburgh. He appears to have got on well there from the very first, as is seen clearly from his letters to his parents. At that time there were several prominent men among the teachers at the University, of whom Monro primus was the leading one. Withering pursued his studies, but also took part in social life; he had literary interests, he played golf, and he was musical and learned to play both the bagpipes and the flute. While he was still a student, Withering gave several short lectures on, *inter alia*, rachitis, angina inflammatoria, and dropsy, before the Medical Association in Edinburgh.

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In the spring of 1766 Withering graduated at Edinburgh, after four years' study, with a treatise entitled "Malignant Putrid Sore Throat." It was written in Latin and dedicated to his maternal uncle, Dr. Brooke Hector, and his first teacher, Henry Wood. As far as can be judged, Withering was at home in that language—he was a member of a Latin club at Edinburgh—but he was never a prominent Latin scholar. In this connection it may be mentioned that, with reference to another language, namely, French, Withering once wrote as follows: "I deem it a heavy task, during the short space of our existence, to be compelled to learn so many signs to indicate the same thing." Like many of the better situated young men of the time, Withering wanted to travel before settling down as a doctor, and he set off with a friend to France. The journey came to an abrupt end, however, for the friend, who was already ailing—probably a victim of tuberculosis—died suddenly; and, after all kinds of difficulties, caused, among other things, by a deficient knowledge of the language, Withering was compelled to return home. He had had time, however, to obtain a lasting impression of Paris, where he had visited hospitals and attended lectures.

The following Christmas Withering spent at home. He was now assisting his father, and, at the same time, he was beginning to look around for some suitable place where he could settle down as a medical practitioner. The doctor in the nearby little town of Stafford had recently died, and, as Withering had just successfully treated a prominent person who lived in the immediate vicinity, Stafford was thought to afford possibilities of a good start for the young man. A hospital for the poor had just been completed at Stafford, and Withering became its first doctor. He never built up a large practice during his time in Stafford, however, and thus his hospital duties and his private practice left a great deal of time on his hands. Withering belongs to the group of historical personages who developed slowly, later to present new and epoch-making ideas with all the greater force and penetration.

Passing by Withering's uneventful early years at Stafford, we find him, at the age of 30, a very busy man, in spite of his inconsiderable activities as a physician. He is studying botany.

In view of the above-quoted letter to his parents, in which he clearly announces his distaste for botany, it is undeniably surprising that it is just this subject that he studies voluntarily, devoting to it every leisure moment and all his energy. As far as the present author has been able to ascertain, there is nothing to indicate that his friend and fellow student Pulteney had any influence on Withering in this connection, but it is quite conceivable that such was the case. This Pulteney was a botanist, and wrote the first English biography of Linné. A more romantic circumstance—quite in keeping with the eighteenth century for the rest—undoubtedly contributed to directing Withering's interest particularly toward the English flora. One of his first patients in Stafford was a young lady, Helena Cooke, who was interested in flower paint-

ing. On his visits Withering used to bring with him flowers which he had picked himself. The young lady subsequently became his wife. There are many descriptions of how it became a habit of Withering's to collect plants and "curious stones" during his long rounds on horseback or by carriage.

Withering married in 1772, and in 1775 he moved to Birmingham to increase his practice and his income. His eldest son, who died in infancy, was born in Stafford, and his daughter Charlotte and his son William were born in Birmingham.

Broling, a Swede, wrote a "Journey to England," in which there is an excellent description of the flourishing industrial town, and also of the forceful and enterprising magnate Boulton, who became Withering's friend and patron. The person who really suggested to Withering that he should move to Birmingham was Dr. Erasmus Darwin, an uncle of the famous Charles Darwin. The suggestion was inspired by kindness, but when Withering's reputation, both as a doctor and a scientist, began to eclipse Darwin's own, this good will was succeeded by persecution and petty annoyances which pained Withering very much. I shall return to this matter in connection with Withering's *digitalis* investigations.

In Birmingham Withering was appointed physician-in-charge at the hospital. He established an outpatient department, and on certain days of the week his private consultations were also open to poor persons. His practice grew rapidly, and in his second year there he earned as much as during his whole eight years at Stafford, but, at the same time, the first evidence of the silent toil of past years presented itself. In 1776 there appeared the first edition of his well-known botanical work, "A Botanical Arrangement of all the Vegetables naturally growing in Great Britain, with Descriptions of the Genera and Species, according to the System of the celebrated Linnaeus." Withering gave a detailed description of each plant, and he sums up thus: "Under each species are added the most remarkable Varieties, the Natural Places of Growth, the Duration, the time and Flowering, the Peculiarities of Structure, the common English Names; the Uses as Medicines, or as Poisons, as Food for Men, for Brutes and for Insects;" and he adds: "With their Applications in Oeconomy and in the Arts." In his preface, in which he goes through all the different points, Withering remarks that many people will doubtless be surprised that he has said so little about the medical uses of the plants. But he considers that they have been abused in this respect, and that superstitious beliefs have led to the use of all sorts of plants for the most varied diseases. On the other hand, he points out that valuable remedies can be prepared from plants. Nothing can better illustrate Withering's own starting point and the contribution he made, as a result of his own investigations into the effects of *digitalis*, than what he himself wrote in the first edition of his *Flora*. "Certain Plants, capable of producing very sudden and remarkable

effects upon the Human Body, are called Poisons. But poisons in small doses are the best medicines, and the best medicines in too large doses are poisonous." Under Foxglove, i.e., digitalis, in the same flora, we find the following remark: "A dram of it taken inwardly excites violent vomiting. It is certainly a very active medicine, and merits more attention than modern practice bestows upon it."

How extensive Withering's practice in Birmingham was, appears from a statement that during one year—1785—his visits to the sick involved travelling more than 6,353 English miles. He made these journeys, which were an extremely great strain at that time, on horseback or by carriage. In order to employ every moment, he had "a light" in his carriage—presumably an oil lamp—so placed that he could read and study during his journeys. Withering's activities as a doctor comprised both those of the hospital doctor and of the very popular practitioner, but yet he found time not only for medical studies, but also for profound botanical, chemical, and mineralogical studies. The period in Birmingham can probably be characterized as the most active period in this ever active man's life.

In 1779 he published a work entitled "An account of the Scarlet Fever and Sore Throat." In the preceding year there had been a severe epidemic of scarlatina in Birmingham, and the disease had also ravaged the whole of England. Withering hoped—as he says in his preface—that his observations would be of use. Scarlatina was often confused with other illnesses. The book attracted much attention in its time. During these and the immediately succeeding years, Withering published several nonmedical papers, *inter alia*, in 1783, an English translation of the Swedish mineralogist Torbern Bergman's "Sciagraphia Regni Mineralis."

At this time there was an illustrious society in Birmingham, the "Lunar Society," of which Withering was elected a member. Through a Mrs. Schimmelpenninck, whose father was also a member of this club, we have very graphic descriptions of the meetings of the club and of its members, among whom—besides its celebrated chairman, Dr. Samuel Johnson—were the Boulton referred to previously, James Watt, the inventor of the steam engine, Joseph Priestley, the English discoverer of oxygen, and the Dr. Erasmus Darwin mentioned above. Many famous men visited the club, *inter alia*, the Swede Solander—Linné's pupil—and Benjamin Franklin. Priestley was a close friend of Withering's and the latter interested himself very much in the new and much discussed discoveries announced by Priestley. He was convinced that Priestley was right, and defended his friend both in speech and writing.

In 1785 Withering was elected a member of the Royal Society, in whose Transactions he published several of his works. In the same year he was also awarded a diploma by the Medical Society of London, and was subsequently (1791) elected to the Linnéan Society. Otherwise he declined the membership of clubs and societies, since, as always, he was

concentrating his time and energies on his work. It was in 1785, also, that he published his work on digitalis, "An account of the Foxglove, etc.," to which I shall devote special attention below.

Withering's reputation, both as a research worker and as a doctor, was now at its zenith. The French botanist, L'Héritier de Brutelle, named a plant *Witheringia solanacea* in his honor. Birmingham was an interesting town in many respects, and to it went many of the foreigners who visited London. Withering's son gives a list of tourists and scholars from Germany, France, Holland, Poland, and Sweden who visited his father, and with whom the latter often carried on a voluminous correspondence.

As early as 1776, Withering had himself noticed the first symptoms of the disease—probably pulmonary tuberculosis—which was to be the cause of his death. Every winter subsequent to that date he had attacks of varying severity. In the winters of 1783 and 1784 he had to give up his practice for long periods and take a complete rest in the country. This is the real reason why, in 1786, he realized his desire to move to the country. He settled down at Edgbaston Hall, outside Birmingham. Nowadays the beautiful hall lies in a suburb of Birmingham, but in Withering's time the district could quite justifiably be described as the country. It was not too far from the town, however, for him to be able to continue to carry on his daily work as a doctor.

At Edgbaston Hall Withering was able, in some degree, to live the country life he had longed for so long. He was interested in the management of the estate, and took a special interest in rearing Newfoundland dogs. Among his pets there were also two monkeys from Gibraltar. One of them died after a few years. Withering followed the monkey's illness carefully—coughing, fever, and wasting. According to Withering, the autopsy revealed "Phthisis pulmonalis similar to that found in human victims." This comment was probably made principally with himself in mind. In 1790 he had an unusually severe pulmonary attack. He began to suffer from breathlessness, and his fatigue made itself felt more and more, but his will to work was still unbroken. He continued many of his works, and to a certain extent carried on his practice. How he suffered because of the feeling that his strength was failing is seen plainly from an utterance quoted by his son in *Miscellaneous Tracts*: "The languor of illness is one of the most mortifying symptoms to those who dislike indolence."

The results of the political unrest which spread to England from revolutionary France contributed indirectly to Withering's failure to improve. Both as a doctor and a private citizen, Withering remained entirely outside political discussions and belonged to no party. His home was threatened during serious riots in Birmingham in July, 1791. Withering tried to save his library and his scientific collections by removing them in wagons loaded with hay. Even though damaged, both

his collections and his home escaped destruction, to which his popularity as a doctor certainly contributed, but the severe mental strain weakened his health further.

Portugal was a holiday resort much favored by Englishmen, especially during the winter, when they wanted to escape from the cold, damp climate of England. In September, 1792, Withering went to Lisbon. During the winter there his health improved to such an extent that he repeated the journey the following year, but not with the same good result. On the contrary, he returned with his strength further reduced. In Portugal Withering studied the subtropical flora and also made water analyses, especially of the hot springs at Caldas da Rainha. His work was published by the Royal Academy in Portugal, of which he was elected a corresponding member. In this connection it may be mentioned that he had already previously—in 1776—translated into English T. Bergman's "De Analysi Aquarium."

Although Withering never had an opportunity of visiting Sweden, he not only met several Swedes, but also cooperated for long periods with Adam Afzelius and Carl Peter Thunberg. Letters are still preserved from the lively correspondence he kept up with these two Swedish botanists. They contributed to a great extent to the working up of the third, much larger edition, of Withering's "Botanical Arrangement," which appeared in 1796 (a quotation from Thunberg appears on the flyleaf).

After his return from the last journey to Portugal, Withering spent most of his time in his library, which he tried, by means of various contrivances, to keep at a constant temperature of about 18° C. In spite of everything, however, Withering was more and more troubled by breathlessness, and at times he had hardly strength to sit writing at his desk. He began to think that Edgbaston Hall, where he had always been so happy, was unsuitable on account of its exposed position, and decided to move to Dr. Priestley's former home. He had the house, which had been almost entirely destroyed by revolutionaries during the period of unrest, carefully repaired.

He never found the relief which he had hoped for so much. On September 28 he moved to his new home, "The Larches," but only eight days later he passed away, on October 6, 1799.

Withering was buried in the old church at Edgbaston. On the tablet of black marble, in addition to the name and particulars, a poem was engraved in the taste of the period, but on the base of the tablet Withering's work is symbolized better than by many words. The emblem of Aesculapius, the serpent-wreathed staff, is sculptured, surrounded by flowering digitalis and *Witheringia solanacea*, cut from living specimens.

Withering's most lasting contribution was undoubtedly his fundamental work on the use of digitalis as a remedy, and therefore that work will be dealt with in detail.

The use of digitalis as a medicinal plant can be traced both among the Irish monks and in Germany, where it appears to have been cultivated as early as in the time of Charles the Great. In 1546 a drawing of it was made by Hieronymus Bock. Leonhard Fuchs gave it its Latin name. After Fuchs' time there are no particulars of its use in German-speaking countries up to Withering's days. On the other hand, in England it was mentioned occasionally before his time (Gerarde, 1597, Parkinson, 1640), and it was used as a remedy for illnesses of the most varied kinds, such as epilepsy, sores, swellings, and vertigo. Digitalis was included in the London pharmacopoeia in 1650.

That the knowledge of digitalis was confined especially to England may be due to the fact that it is a very common flower and grows in great profusion there.

As is well known, Withering was a skilled and meticulously observant physician, as well as a learned botanist. In his book "An Account of the Foxglove, and some of its Medical Uses, with Practical Remarks on Dropsy," he describes how his interest in digitalis was first aroused. In 1775 he was questioned about an old prescription for the cure of "dropsy" with which "an old woman" in Shropshire was said to perform miracles after doctors had failed. The old woman's prescription proved to be compounded of twenty different herbs, but it was not difficult for Withering—as he says himself—to discover that digitalis was the effective ingredient. It had been used as an emetic and a laxative, but its influence on the heart and its diuretic effect had clearly not even been noticed. In the preface to his book, Withering says quite modestly that he had often been urged to write about digitalis, and equally often had refused to do so, but finally, with hesitation—however incompetent he felt himself—he had decided to take up his pen. What really led to Withering's publication was as follows, as he expresses it himself: "The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable." Ten years' experience with digitalis as a diuretic, tested on a comprehensive material, comprising 163 of his own cases of "dropsy" and the experiences of various doctors, forms the basis of Withering's classic work, in which he presents his results with extreme objectivity. Case after case is described in the most concise form possible, with the histories and physical signs, and with day-to-day notes on the effects of the drug. In many cases its diuretic effect was extremely striking. Only a few days' use of the remedy was sometimes sufficient to cause the edema to disappear. In other cases of dropsy, again, results were insignificant or completely absent. If the histories of the different patients are studied, it will be found that, as a rule, Withering succeeded in getting the diuresis started in the cases in which there were both edema and asthma, i.e., difficulty

in breathing during rest or on exertion; in other words, in cases of what we usually call chronic cardiac insufficiency. Withering gives particulars of only one case from the year 1775. After 10 days' treatment with a decoction of digitalis, large quantities of water had been excreted, the difficulty in breathing had receded, and the general condition was improved.

From the following year he reports four cases, of which No. IV is remarkable in several respects, and is given in detail here. On July 25, 1776, Withering was consulted by Dr. Erasmus Darwin—the older colleague who had advised Withering to move to Birmingham—about one of Darwin's patients. A middle-aged married woman was suffering from extremely troublesome dyspnea; her pulse was weak and irregular, her arms cold and clammy. She had troublesome orthopnea and could not lie down in bed. She had considerable edema in her legs, thighs, and over the abdomen, and passed extremely small quantities of urine. It had been proposed to scarify her legs but the proposition was not acceded to. Dr. Darwin had tried, *inter alia*, antispasmodics, diuretics, and laxative remedies, without result. Withering then pointed out: "In this situation I knew of nothing likely to avail us, except the Digitalis: but this I hesitated to propose, from an apprehension that little could be expected from any thing; that an unfavourable termination would tend to discredit a medicine which promised to be of great benefit to mankind, and I might be censured for a prescription which could not be countenanced by the experience of any other regular practitioner. But these considerations soon gave way to the desire of preserving the life of this valuable woman, and accordingly I proposed the Digitalis to be tried; adding, that I sometimes had found it to succeed, when other, even the most judicious methods, had failed. Dr. Darwin very politely acceded immediately to my proposition, and, as he had never seen it given, left the preparation and the dose to my direction." Fol. Digitalis was prescribed; within twenty-four hours diuresis started, and 9 liters of urine were excreted. An appreciable general improvement set in, the dyspnea was relieved, the pulse became stronger and more regular, and the edema in the legs disappeared. After that Darwin and Withering looked after the patient alternately until September 10, when Withering took her over entirely. Nine days later, on September 19, the edema had begun to return, and another course of digitalis was begun, with the same brilliant results as on the first occasion. At the end of his description Withering says that he attended this woman for nine years, and gave periodical courses of digitalis which obviously prevented the edema from developing to any more appreciable extent. He adds that, for this, "very small doses" are required. The case illustrates the almost miraculous effect of digitalis. The remedy not only saved this woman's life in the more acute stage, but in small doses it kept her alive for nine years, and prevented edema. Our conception of its value as a therapeutic agent in the treatment of

chronic cardiac insufficiency has not changed to any considerable degree since Withering's days. The following lines by Withering, which conclude the description of this case, are of very special interest: "I have been more particular in the narrative of this case, partly because Dr. Darwin has related it rather imperfectly in the notes to his son's posthumous publication, trusting, I imagine, to memory, and partly because it was a case which gave rise to a very general use of the medicine in that part of Shropshire."

According to Professor John Fulton, of Yale University, who attempted to elucidate the priority as regards the discovery of the therapeutic value of digitalis, Erasmus Darwin's formal priority is clear, for, in an addendum to his son's doctor's dissertation, he published as early as 1780 an account of some patients with "dropsy" who were successfully treated with digitalis. In January, 1785, he published in *Medical Transactions* his second study on the subject. Withering's "Account of the Foxglove" is dated in July of the same year. However, Darwin's procedure in this matter can be looked upon as none too punctilious according to modern conceptions, for Withering's description, as given above, is considered fully verified, and thus Darwin learned about the effect of digitalis for the first time from Withering, in 1776. Withering's ethical priority is thus absolute.

In any case, the news of Withering's therapeutic successes with digitalis spread far and wide in England. He received large numbers of letters from colleagues, full of praise for his observations, and some of these letters are reproduced in his book.

Withering had not only collected an abundance of cases in which dropsy had been successfully treated, but had also made detailed studies of the purely botanical features of this remarkable plant, and in his book a beautiful colored reproduction of a specimen of digitalis, with its purple, bell-like flowers, appears. In a special chapter he gives advice as to the preparation of the drug. In the first place, the leaves should be collected just at flowering time and then dried. Withering prescribed that, as a rule, the leaves should be pulverized, and the medicine given in the form of an extract, infusion, or powder, as pills or tincture, but he says rightly: "But the more we multiply the forms of any medicine, the longer we shall be in ascertaining its real dose." With regard to the dosage, it is amazing how little Withering prescribed: "1-3 grains (0.12-0.36 gram) twice daily," which amount tallies extremely well with that used by doctors to this day. On the other hand, his predecessors, the quack doctors, used considerably larger, nay, dangerous doses, against which Withering gives a very special warning. As a drastic example of such overdosing, even by his colleagues, Withering mentions that a Dr. Cawley himself took twelve times the above-mentioned dose, but that he must have had an unusually strong physique, for otherwise he would have died of digitalis poisoning. Withering was very well acquainted with the symptoms of poisoning from digitalis, and

describes them in detail as follows: "The Foxglove, when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as thirty-five in a minute, cold sweats, convulsions, syncope, death." Withering advises a continuance of the proposed daily doses until the drug has affected either the kidneys, stomach, pulse, or intestines, but that it shall be discontinued as soon as symptoms from any of these organs make their appearance. From a study of Withering's book on digitalis, it appears clear that Withering undoubtedly discovered its strong diuretic effect; previously the drug had been known only as a laxative and emetic, probably because the medicine had been given in overdoses.

Withering sums up his conclusions on the diuretic effects of digitalis in eight points at the end of the book, but adds a ninth point which is particularly worthy of attention, and therefore I quote it here: "That it has a power over the motion of the heart to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends."

It was not sufficient that, during a period of ten years, Withering, with his extraordinary powers of observation and his critical penetration, established the fact that digitalis is above all an unsurpassed diuretic, but he also discovered its extraordinary effect on the heart and its movements. In a number of his case histories he remarks particularly that, during treatment with digitalis, the action of the heart becomes slower. Withering was the first to establish the specific effect of digitalis on the heart, an observation which modern physicians consider the most important and self evident. In Withering's time, "dropsy" was a morbid state in which digitalis was sometimes efficacious, and sometimes not, as he very correctly points out. Today it is known that dropsy is a symptom of different conditions, such as kidney diseases, diseases of the liver, and, especially, cardiac insufficiency, and that it is only with the latter form of dropsy that digitalis is a specific remedy because of its effect on the heart. Without being in a position to make this classification of dropsy, Withering describes—as has been pointed out above—cases of successfully treated dropsy, the symptomatology of which he describes with unusual acumen, and which in our time would be diagnosed as cases of typical cardiac insufficiency.

At first, Withering's digitalis treatment did not attract any considerable attention within the medical world. Neither Corvisart, Napoleon's court physician, nor his pupil, Laennec, devoted any great interest to digitalis, although they were among the outstanding figures in medicine, and for over fifty years digitalis was very little used as a cardiac medicine. In 1798, Hahnemann, the founder of homeopathy, spoke extremely skeptically and sarcastically about digitalis as a medi-

cine. It was the German clinicians—first, Kreysig, in 1814, and, subsequently, Ludwig Traube, in 1864—who became interested in the use of digitalis for heart disease. Traube established, in the first place, that digitalis had a regulating effect on the rhythm of the heart, and that it reduced the heart frequency. Leyden (1881) and Nothnagel (1878) arrived at the conclusion that digitalis was our foremost remedy for the treatment of cardiac insufficiency, and its clinical use was first elucidated by these research workers and their contemporaries, James Hope and William Stokes. The knowledge of digitalis was greatly widened by Homolle, Quevenne, and Nativelle, and, above all, by the fundamental work of Schmiedeberg, the German pharmacologist, in 1875. These investigators, in the first place Schmiedeberg, attempted to isolate the active substances, which were called glucosides, from the digitalis leaves. Later, all over the world, innumerable pharmacologists began to test these substances which affected the heart by means of experiments on animals, and established the principle for the pharmacologic effect of the so-called cardiac glucosides. Broadly speaking, the experiments on animals taught that digitalis evoked a stronger contraction of the heart muscle.

It might be said that full justice had not been done to Withering's pioneer work until during the last fifty years. Clinicians in all countries now see in digitalis the pre-eminent heart remedy, which has the power to relieve cardiac insufficiency and strengthen the failing heart; which in countless cases actually performs miracles, and helps persons with heart disease of various kinds to live an endurable life for years, nay, perhaps decades. Mackenzie and his pupil, Lewis, and Warburg are of the opinion that, on the whole, digitalis affects only cardiac insufficiency with congestion, and is useful, above all, in cases in which auricular fibrillation is present. The physician of today knows that in the typical case of cardiac insufficiency, with all its cardinal symptoms, such as dyspnea, a swollen liver, edema, and a rapid, irregular pulse, there is often a prompt response to digitalis, with increased diuresis, reduced pulse frequency, an even, regular pulse, a reduction of the liver swelling, and increasing working capacity. In spite of the enormous progress that physiology has made during the last 30 years, and the employment of physiologic methods in the cardiac clinic, it has not yet been possible to establish with certainty whether digitalis increases the amount of blood the human heart pumps per unit of time, i.e., its minute volume. In 1938, I found that, in cases of congestive heart failure, digitalis instantaneously leads to an increased oxygen consumption by the patient, which probably implies that the blood flow increases, i.e., that the minute volume of the heart increases. Further, I have shown that digitalis may increase the performance capacity, as measured with my function test, in latent cardiac insufficiency, i.e., in cases in which objective signs of heart failure are absent when the patient is examined during rest.

By means of modern electrocardiography we are today able to establish that digitalis can eliminate flutter and fibrillation, the presence of which may be the cause of both an extremely rapid and an irregular action of the heart. Such rapid contractions of the auricle, 300 to 600 times per minute, which are extremely wasteful with respect to the work of the heart, may at times be checked by the administration of digitalis, and be followed by normal sinus rhythm at a rate of 60 to 80 beats per minute. Very frequently, neither flutter nor fibrillation can be eliminated by digitalis, but nevertheless the remedy—and this is extremely usual—blocks the transmission of these waves to the ventricles, so that perhaps only a fraction of the waves are transmitted, and the work of the heart is thereby facilitated.

Innumerable preparations of digitalis have seen the light of day. The original digitalis leaf, in powdered form, still retains its place, however. Of the preparations in more or less pure form, emanating from firms all over the world, "Digalen" is probably one of the best known. In Sweden we have had "Digitol" for a decade, and, during recent years, "Digiton." Research and industry have proceeded hand in hand on this subject, and the last word has probably not been said as to the effect of the different constituent elements of the digitalis leaf. Commissions have been set up to study these questions, and attention must be drawn in particular to the Dutch Commission, which was entrusted with the task of cooperating with prominent experts, physicians, and pharmacologists in investigating the effects of digitalis. The work of the Commission was published in book form in 1923, and, in the introduction, it is said that if Withering's monograph is compared with what has been written about digitalis during recent years, the volume of the latter is amazing, but unfortunately there is very little new in it which is of undisputed importance in practice and which had not already been given in Withering's classic work.

Thanks to indefatigable efforts, Emil Hultmark, Ph.D., has succeeded in tracing the portrait of Withering by the Swedish artist, F. von Breda, and it now has a place in the National Museum in Stockholm.

Breda painted the portrait in Withering's home, Edgbaston Hall, in 1792. The resemblance is said by his son and one of his friends to have been striking. The position, the expression round the mouth, and the hand which nonchalantly, yet constrainedly, grasps some sprays of digitalis, conform well with the picture Mrs. Schimmelpenninck gives us of Withering. As has been mentioned above, her father and Withering were members of the Lunar Society. She describes Withering as friendly but reserved and uncommunicative; esteemed as he was, he never was among the really popular members of the Society. In the portrait, an unconscious nobility rests on the well-shaped forehead, the long nose, and brushed back, slightly powdered hair. Withering is said to have been very particular about his attire. It is true that at

that time it was the custom always to paint so-called beautiful hands, but one likes to believe that the elegant hand holding the digitalis resembled Withering's own. Finally, with his colors and his brush work, Breda has managed to hand down to us something of the strength and acuteness of intellect which were characteristic of William Withering.

I wish to proffer my warm thanks for their interest and ready cooperation to Dr. Emil Hultmark, and especially to Dr. Erik Waller. Dr. Waller kindly placed at my disposal both his eminent learning and his private library.

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ANGIOCARDIOGRAPHY AND ITS VALUE

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ANGIOCARDIOGRAPHY as a method of cardiovascular exploration was presented by two of us (Dr. A. Castellanos and Dr. R. Pereiras, with Dr. A. García) toward the end of 1937, after it had been employed for many months on our cardiac patients. Since that time we have used it systematically in the examination of cardiac patients, and it has become a routine, for it proved to be quite harmless and its diagnostic value surpasses by far that of any other method.

After our work, Steinberg and Robb, of New York, applied the same method to adults with extraordinary success. They performed hundreds of intravenous injections of the opaque substance at high speed without any accident.

Is the word "Angiocardiography" a new medical term? W. A. Newman Dorland, member of the Committee for the Nomenclature and Classification of Diseases of the American Medical Association, has recognized the word "Angiocardiography" as a new scientific term, and included it in the 1941 edition of the American Illustrated Medical Dictionary. *Angiocardiography* means roentgenographic visualization of the heart cavities and large communicating vessels by means of a radiopaque substance. In 1936, several French authors, among whom Ameuille is remembered best, employed the method heralded by Moniz, of Lisbon, of injecting the contrast medium through a catheter which had been introduced as far as the right auricle, and in this way obtained roentgenograms in which the right auricle and ventricle and the trunk of the pulmonary artery were visualized. For this purpose they employed a 120 per cent solution of sodium iodide. However, the difficulties of catheterization of the auricle, as well as the great toxicity of the large amount of iodide, compelled these authors to state that the method could not be employed routinely.

Our first work on angiocardiography was done in 1931, and in 1937 we devised an easy, harmless technique which we have continued to use until the present time. Angiocardiography is a strictly original method, for, previous to the work of Castellanos and Pereiras, no attempt had been made to use peripheral veins for visualizing the human heart cavities and their large communicating blood vessels.

What is the purpose of angiocardiography? It was devised with a view of establishing correct diagnoses of congenital heart disease. *Post-*

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Fig. 1.—Normal angiocardioagram, anteroposterior view; newborn child.



Fig. 2.—Normal angiocardioagram, lateral view; baby, 4 months old.

mortem angiocardiology is performed in cases in which autopsy is refused; it provides distinct images, when carried out with an adequate technique, and its diagnostic value is as great as that of angiocardiology in the living subject. Moreover, angiocardiology furnishes many valuable data in other conditions, such as situs inversus, mediastinal displacement, etc.

How is an angiocardigram obtained? The technique of the method is very simple, and consists of two main stages:

- (1) Introduction of a thin Lindeman trocar in a vein of the elbow, hand, leg, or thigh.
- (2) Injection of the radiopaque substance and exposure of the x-ray film at the end of the injection.



Fig. 3.—Interventricular communication, with slight stenosis of pulmonary artery. Anteroposterior view.

The gauge of the trocar will vary according to the development of the venous system of the patient and his age. The quantity of contrast medium to be injected depends not only on the age and weight of the patient, but also on the presence or absence of cyanosis, because the more pronounced the cyanosis the greater will be the quantity of radiopaque substance required for obtaining proper contrasts. On an average, 8 to 10 c.c. are employed in a newborn child, and 12 to 20 c.c. in an infant. In older children, the quantity will vary between 15 and 30 c.c.

Although sodium iodide should never be used in the living, there are many other substances, such as per-abrodil, uroselectan, hippuran, etc.,



Fig. 4.—Total transposition of the large vessels. Anteroposterior view. The aortic shadow is very dense because the artery is arising from the right ventricle.



Fig. 5.—Persistence of left superior cava. Left auricle visualized. Interventricular communication. Aorta and its branches visible. Hypoplasia of pulmonary artery. Below the cardiac shadow lie the inferior cava and suprahepatic veins.

which give satisfactory results when employed in concentrations of 35 to 70 per cent. The injection must be carried out within one and one-half to two seconds.

From birth until six months of age we use a 35 per cent solution of the radiopaque substance. From six months until two or three years



Fig. 6.—Interventricular communication. (Partial agenesis of septum.) Pulmonary stenosis. Anteroposterior view.



Fig. 7.—Tetralogy of Eisenmenger. anteroposterior view. Interventricular communication. Dextroposition of the aorta, which arises above the defect. The pulmonary artery is normal.

of age we may use the same solution in noncyanotic patients, but, in the presence of cyanosis, the best concentration is 50 per cent.

The injection of the radiopaque substance must be completed as rapidly as possible, and the roentgenogram made before the syringe is entirely emptied, i.e., when it still contains two or three cubic centimeters of the solution.

It is possible to obtain anteroposterior and lateral views with a single injection by employing two x-ray tubes and two films.

We employ a special apparatus which permits automatic injection into the vein and exposure of the film at the right moment, without any other manipulation on the part of the operator. It is also advisable to use a special arrangement for maintaining complete immobilization of even the most unruly patient.



Fig. 8.—Congenital dextrocardia, anteroposterior view. Very large interauricular and interventricular communication.

What is an angiocardigram? A normal angiocardigram is easily interpreted, be it an anteroposterior or lateral view. In the anteroposterior view the axillary and subclavian vein, the corresponding brachiocephalic vein stem, the right auricle and ventricle, the stem and branches of the pulmonary artery, and sometimes even the thinnest ramifications of the pulmonary artery become apparent. Usually, the image is U shaped. In the lateral view, the same structures are seen, especially the pulmonary artery as it passes in a semicircle from the infundibulum to its site of bifurcation.

Pathologic angiocardigrams are very interesting, and some amount of experience will permit their correct interpretation. Stenosis of the

pulmonary artery produces a characteristic image which enables one to differentiate the orificial and the infundibular type. It also reveals the extent of the malformation. Patency of the interventricular septum may be diagnosed by indirect signs, such as indentation of the border of the right ventricle, the presence of radiopaque substance within the left ventricle, or sometimes directly by visualization of the communication itself. Transposition of the large vessels, Fallot's tetralogy, and interauricular communications are likewise revealed by characteristic features. In some instances one can also detect patency of the ductus arteriosus by direct or indirect signs. In other cases the method reveals gross malformations of the septum or the presence of a single auricle or ventricle. A single arterial stem produces a typical shadow which indicates common origin of the aorta and pulmonary artery.



Fig. 9.—Large interventricular communication. The aorta is deviated to right side over the right bronchus (Corvisart type).

Is angiocardiology harmless? The experimental work of Reboul, Racine, Contiades, Ungar, and Naullau proves that the dosage employed by us is quite harmless. This has also been corroborated by the recent work of Robb and Steinberg. We have never seen any serious angiocardigraphic accident since we began to employ the method three years ago. Robb and Steinberg have had the same experience in a series of about a hundred injections. We wish to emphasize that we have employed the method in the preagonal and agonal stages of heart disease. We do not refer to cases of heart failure or grave cardiac insufficiency, for almost half of all patients studied by us had reached this stage.

The value of angiocardiology. It is the most accurate method of cardiovascular exploration used at present for the diagnosis of congenital heart disease. It does not furnish indirect evidence, as is the rule with electrocardiography, radiokymography, orthodiagraphy, tele-radiography, phonocardiography, and blood gas analysis, but direct anatomic information concerning the chambers of the heart and the great vessels.

When we started our research we made post-mortem angiocardio-grams, and then, at autopsy, studied the relations between the images and the deformities. Later, in the course of the last three years, we have continued to perform autopsies on patients on whom we had obtained angiocardio-grams during life. This procedure has shown that angiocardio-graphic diagnoses are surprisingly accurate, for, in every instance, the roentgenogram was characteristic of whatever vascular deformity or abnormality of the septa happened to be present.

Dr. J. M. Martínez Cañas, our eminent cardiologist, remarked in the course of a discussion of our investigations at the Cuban Society of Cardiology that angiocardiology was a method of doing an autopsy on the living.

Dr. Pedro L. Fariñas, in one of his last papers, says that the angiocardio-graphic method of Castellanos and Pereiras has revolutionized the diagnosis of congenital heart disease.

Other methods derived from angiocardiology. Angiocardiology has given rise to other methods, such as visualization of the inferior and superior venae cavae, and, above all, to retrograde aortography, or aortography by countercurrent. This is a special method for diagnosis of patency of the ductus arteriosus, and consists mainly in introducing a thin trocar into the left brachial artery, maintaining an Esmarch ligature below or behind this site, and injecting a radiopaque substance. The contrast medium passes in a retrograde, or centripetal, direction into the left subclavian artery and the arch of the aorta, and the latter stands out in great contrast. If there is patency of the ductus arteriosus, some of the contrast medium appears in the pulmonary artery after having passed through the ductus arteriosus itself.

CONCLUSIONS

1. We were the first to demonstrate that the heart cavities and great vessels can be visualized by injecting a radiopaque substance into a peripheral vessel.
2. This procedure, which we call angiocardiology, is the most accurate method for diagnosing cardiac abnormalities.
3. The technique is easy, and it can be done wherever there is roentgenographic equipment.
4. The interpretation of normal and pathologic angiocardio-grams does not present any difficulties.
5. In view of its rapidity and accuracy, angiocardiology is indispensable in the study of heart disease.

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THE SEROLOGIC REACTION IN CARDIOVASCULAR SYPHILIS

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WHENEVER the clinician is confronted, in differential diagnosis, with cardiovascular syphilis, the question immediately arises: How often is the serologic reaction positive in syphilitic heart disease? That the answer to this query is usually not very clear is a reflection of the indefinite state of affairs which exists in regard to the serologic situation in cardiovascular syphilis. The study presented here was undertaken to clarify this point. In addition, an attempt was made to ascertain what other criteria may be of aid, beyond those now known, in making a correct clinical diagnosis of cardiovascular syphilis.

Since the Wassermann reaction was first described, over thirty-five years ago,¹ its aid in the diagnosis of syphilitic heart disease has been invoked. However, a glance at the literature (Table 1) regarding the incidence of positive serologic tests shows a wide discrepancy of figures. The reasons for this are several. First, in numerous reports the percentage of seropositivity has been arrived at by ascertaining its incidence in cases in which the clinical diagnosis was cardiovascular syphilis. Although the clinical diagnosis of aneurysm and aortic insufficiency can be made in many cases with a fair degree of certainty, this becomes an entirely different matter in cases of uncomplicated aortitis. In a paper published in 1932, Moore, Danglade, and Reisinger² listed certain criteria for the clinical diagnosis of aortitis, but further review of their diagnostic points did not substantiate the conclusions they had reached.^{14, 19, 20} The diagnostic criteria set up by Maynard²¹ may be an answer to this problem, but so far not enough data have been accumulated to be convincing. It may therefore be asserted that at present the diagnosis of uncomplicated aortitis is generally considered impossible.

Second, another source of error in accepting the figures in the literature lies in the fact that the sensitivity of the Wassermann reaction has undergone frequent and marked changes. Increasingly sensitive tests have been added to our serologic armamentarium. We find that practically all studies have included a large percentage of cases dating back to an era in which the Wassermann test, by modern standards, was quite insensitive. Such reports can therefore be only misleading when the incidence of seropositivity in cardiovascular syphilis at the present time is considered.

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TABLE I
THE WASSERMANN REACTION IN CARDIOVASCULAR SYPHILIS (HISTORICAL REVIEW)

SEROLOGIC TEST	AORTITIS		AORTIC INSUFF.		ANEURYSM		EXACT DIAGNOSIS OR HISTORY OF TREATMENT NOT SPECIFIED	YEAR	DIAGNOSIS	AUTHOR
	TREATED	NOT TREATED	TREATED	NOT TREATED	TREATED	NOT TREATED				
Not specified							57.5%	Up to 1923	Clinical	Stokes and Anderson ²
Kahn							81.8%	1929	Clinical	Miller ³
Kline							84.8%	1929	Clinical	
Not specified	75%							1910-1930	Pathologic.	Moore et al. ⁴
Not specified	65%			68%		83%		Up to 1930	Pathologic.	Willius ⁵
Not specified							76%	1912-1930	Pathologic.	Reid ⁶
Wassermann (water bath)							85%	1920-1930	Clinical	Eagler
Wassermann (icebox)							95%	1920-1930	Clinical	
Wassermann (i.b.) or Eagle							95-100%	1920-1930	Clinical	

Wassermann				93%		Up to 1931	Clinical	Carter and Baker ⁸
Wassermann				“Nearly 93%”	“Nearly 93%”	Up to 1931	Pathologic.	Carter and Baker ⁹
Not specified						Up to 1934	Pathologic.	Scott ¹⁰
Not specified	52%	83%				Up to 1936	Clinical	Cole and Usilton ¹¹
Not specified			85%			Ditto	Clinical	Cole and Usilton ¹²
Not specified				45%	90%	Ditto	Clinical	Cole and Usilton ¹³
Wassermann, Hinton, or both	90%					Up to 1937	Pathologic.	White and Wise ¹⁴
Kahn	About the same percentage in all three categories					Up to 1938	Clinical	Wile and Snow ¹⁵
Wassermann						Up to 1940	?	Gager ¹⁶
Wassermann or Kahn	70%		95%	95%		1940	Pathologic.	Gouley and Anderson ¹⁷
Wassermann				98%		1936-1940	Clinical	McDermott et al. ¹⁸

Third, the question of treatment previous to study is one frequently not mentioned, a point which admittedly may be of great significance.

And, fourth, a history of a previously positive serologic reaction or a history of previous antisyphilitic treatment might be of great aid in making a diagnosis.

This report presents a review of 100 consecutive cases of cardiovascular syphilis, *diagnosed at autopsy*, in which the histories provided adequate data for study. These cases were for the most part from the Stanford Medical Service of the San Francisco Hospital, although six had been patients at the Stanford Medical Service at Laguna Honda Hospital, the chronic disease division of the San Francisco county institutions. These patients came to necropsy between March 1, 1933, when the laboratories of the San Francisco Department of Public Health added the Kahn test to the already routine Wassermann reaction, and January 12, 1942. The serologic technique was altered at no time during this period. In the evaluation of serologic positivity there have been included in the seropositive group all those cases in which there was a positive Wassermann or Kahn, or both.

In a survey of the data, we find, in contrasting the varieties of lesions, that there was no essential difference in the distribution of aortitis, aortic insufficiency, and aneurysm between the seropositive and the seronegative group.

In studying the effect of previous antisyphilitic treatment on the Wassermann and Kahn reactions (Table II), the figures suggest that therapy is only of moderate importance.

TABLE II
EFFECT OF TREATMENT
ON SEROLOGIC REACTION IN CARDIOVASCULAR SYPHILIS

TREATMENT	SEROPOSITIVE GROUP 87 CASES	SERONEGATIVE GROUP 13 CASES
"Much"	10%	31%
"Little" or none	73%	62%
Uncertain or unknown	17%	7%

"Much" treatment—twenty or more injections of a trivalent arsenical and a corresponding amount of bismuth.

"Little" treatment—less than this amount.

The average age in the seronegative group was 69, as against 55 in the seropositive, which is perhaps an indication of spontaneous arrest.

In view of the small number of cases in the seronegative group, the data thus far can be taken merely to indicate a trend. Because we think that the clinical diagnosis of syphilitic aortitis in the uncomplicated form is still impossible, the figures in Table III concerning the incidence of positive reactions in uncomplicated aortitis are, for the present at least, merely of academic interest. Despite the high incidence of positive Wassermanns (86 per cent), the clinical diagnosis of aortitis

TABLE III

THE INCIDENCE OF A POSITIVE SEROLOGIC REACTION IN CARDIOVASCULAR SYPHILIS

PATHOLOGIC DIAGNOSIS	NO. OF CASES	SEROPOSITIVE	SEROPOSITIVE OR HISTORY OF POSITIVE SEROLOGIC REACTIONS OR HISTORY OF TREATMENT
Aneurysm or aortic insufficiency or both	49	43 (88%)	47 (96%)
Uncomplicated aortitis	51	44 (86%)	46 (90%)

was not made in a single instance. However, the figures may be of some importance because they are at variance with the statement of Gouley and Anderson,¹⁷ who said, in 1940, that "it is now well known that the Wassermann and Kahn tests are negative in about 30 per cent of the patients who at necropsy exhibit syphilitic aortitis."

In aortic insufficiency and aneurysm, the diagnosis is made with considerable certainty in many instances, but at times the clinical problem is very vexing. Therefore, our data are of particular interest.

In Table III the clinically diagnosable group of cases, namely, those with aneurysm and aortic insufficiency, has been separated from those of uncomplicated aortitis. Of the 49 cases in this former group, in 43, or 88 per cent, there was a positive Wassermann or Kahn, or both, on the first examination. However, when to this figure we add those seronegative patients who gave a history of a previously positive test or of previous antisyphilitic treatment, the percentage total increases to 96 per cent. This is important because a history of previous antisyphilitic treatment or a previously positive serologic reaction is information that is readily obtainable from the patient and is not subject to individual misinterpretation such as a "history of syphilis" which may in reality represent lymphopathia venereum or a mere herpes genitalis.

SUMMARY AND CONCLUSIONS

A study of 100 cases of cardiovascular syphilis, *diagnosed at autopsy*, in which the serologic reactions had been done by a modern technique, is presented. Of 49 cases of aortic insufficiency or aneurysm or both, in 43, or 88 per cent, there was a positive Wassermann or Kahn or both on first examination. Of 51 patients with uncomplicated aortitis, 86 per cent had a positive serologic reaction. In none of the cases of aortitis was the diagnosis made clinically.

Of the 49 patients with clinically diagnosable cardiovascular syphilis, i.e., aortic insufficiency or aneurysm or both, 96 per cent had either a positive Wassermann or Kahn or both, or a history of a positive Wassermann in the past, or, lastly, a history of previous antisyphilitic treatment.

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AN APPARENT CAUSAL MECHANISM OF PRIMARY THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEINS

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THROMBOSIS of the axillary and subclavian veins may be caused by infection of regions adjacent to, or drained by, these veins, by invasion or compression by neoplastic tissue, by direct external trauma, or by some unknown mechanism related to forceful or sustained motion of the shoulder girdle or arm on the affected side. The diagnostic term, primary or effort thrombosis, is applied to the cases that fall into the last group, and it is with this group that this paper is solely concerned.

Although the literature on primary thrombosis of the axillary and subclavian veins is increasing, and excellent reviews on this subject have been published by Matas,¹ Hammann,² and others, the condition is not common. In most instances only single cases are reported. The eight case histories presented by Gould and Patey³ constitute the largest series investigated by any workers. There has been a singular paucity of reports in the American literature. In this paper, five case histories from the Medical Division of the University of California Hospital are presented, and an explanation of the causative mechanisms is offered.

Paget,⁴ in 1875, described spontaneous thrombosis of the veins of the upper extremity under the classification of "gouty phlebitis," and cited similar cases reported by Mackenzie, in 1862, and Humphry, in 1869, but the first adequate clinical recognition of the condition is generally credited to von Schroetter,⁵ in 1884. Considerable time elapsed between this report and the general awakening of interest in the condition, beginning in 1911, in Germany, Great Britain, France, and Switzerland.⁶⁻¹⁴

The condition usually occurs in healthy young males who are engaged in vigorous muscular activity, but it may occur at any age from childhood onward,¹⁰ and in either sex. As would be expected, the right arm, because of its more general use, is more frequently affected than the left. Paggi¹² found that the ratio of involvement of the right arm to the left was 2.5 to 1. The onset may be heralded by pain in the shoulder or arm, or it may be painless. Turgidity and edema may develop in the arm immediately after the suspected causative effort, or hours or days may elapse between the apparent cause and the signs of a thrombosed vein. The skin is usually cyanotic; the superficial veins of the arm and the collateral veins of the shoulder and upper part of the chest

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are often distended within a few hours after the onset of edema. The venous pressure has been found by Veal¹⁶ to be elevated; both he and Cottalorda¹⁷ reported elevated systolic and diastolic brachial arterial blood pressure on the affected side. A palpable, tender cord is often felt in the region of the brachial and axillary veins shortly after the onset of signs and symptoms. Local signs of inflammation rarely are found. With rest of the extremity, the edema and stiffness may subside in as short a time as five days, but they usually last from two to eight weeks, and often recur with active use of the arm for five or six months and occasionally for as long as six years.¹⁸ Operative removal of the thrombus has been advocated in order to facilitate more rapid recovery.^{1, 15, 19}

The types of precipitating effort vary considerably, and may be classified as follows:

- Type 1. No unusual effort or motion.^{3, 16, 20, 21, 22}
- Type 2. Lifting of heavy weights.^{1, 23-26}
- Type 3. Long sustained and moderately vigorous activity involving the arm or arms and shoulder girdle:
 - a. Holding a high-spirited riding horse with the left hand (left arm involved).⁷
 - b. Holding back a team of driving horses.²⁷
 - c. Rowing a boat.²²
 - d. A police officer struggling to hold an arrested person.²⁸
 - e. A soldier loading and unloading a piece of field artillery.²⁹
 - f. Long stirring of heavy pudding mixture.³⁰
 - g. Scrubbing clothes for a long time.¹⁶
 - h. Carpentry work, presumably sawing and planing.²⁶
 - i. Throwing a ball or a rock.^{10, 31}
 - j. Playing a strenuous game of golf (left arm involved).³
 - k. Patient pushing himself up in bed.³³
- Type 4. Minimal effort involving frequent or sustained elevation of the arm or arms over the head:
 - a. Screwing in curtain rods high over head.³
 - b. Placing jars on a high shelf.³
 - c. Cleaning a ceiling.³
 - d. Hanging meats on high hooks.¹⁰
 - e. Exercises of elevating arms over head.³²
 - f. Sleeping with arms extended upward under the head.¹⁶

Many cases in which no precipitating effort was reported may have been examples of Type 4. A careful history perhaps would have revealed a period of unusual elevation of the arms.

Five cases of primary thrombosis of the axillary and subclavian veins are presented.

CASE 1.—(Figs. 1 and 2). D. R. J., 30 years of age, was a broad, moderately deep-chested, right-handed, healthy appearing man whose natural posture was such that the shoulders were held back and the clavicles were directed upward and posteriorly. He entered the University of California Hospital November 6, 1940. One week earlier, after pitching a baseball, he had noted a pulling pain in the right axilla and the deltoid region, followed by mild soreness which disappeared completely within twelve hours. On the next day the entire right arm felt numb for five minutes after

he had pitched a baseball. He noted tenderness on pressure in the right axilla for a week, but pain did not recur until the day he entered the hospital. About four hours prior to entry, after playing a set of tennis, he noted swelling of the right forearm. After he had played two more sets he noted that his entire right arm was



Fig. 1.

Fig. 1.—Infrared photograph of patient in Case 1. Illustrates the swelling of the affected right arm and the distended superficial veins of the arm, shoulder, and pectoral region. The broad chest and posteriorly directed clavicles are evident. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

Fig. 2.

Fig. 2.—Roentgenogram of the upper chest and shoulder in Case 1. The high, widely sweeping first ribs and the posteriorly directed clavicles are illustrated. (Reproduced from Medico-Surgical Tributes to Harold Brunn.)

swollen and cyanotic, and he felt an aching pain and numbness throughout the arm from the shoulder to the hand. The pain disappeared in half an hour.

Physical examination revealed that the posterior curvature of the right clavicle was greater than that of the left. The entire right arm, to the shoulder, was swollen, cyanotic, and moderately indurated. The superficial veins of the hand and arm, as well as the superficial collateral veins over the shoulder and upper right pectoral region, were dilated. A tender, firm cord extended from the region of the brachial vein into the right axilla. At time of entry the blood pressure was 135/75 in the left, and 140/70 in the right, arm. After complete rest of the right arm for six days, the blood pressure was 124/60 in the right, and 134/70 in the left arm, and the swelling and cyanosis had subsided. At time of entry the rectal temperature was 38.4° C., and the leucocyte count was 12,000; both returned to normal within six days. At time of entry, the venous pressure in the left arm was normal; the veins in the hand collapsed at about the level of the third rib when the patient was in the erect position. The venous pressure in the right arm was elevated; the veins in the hand collapsed 30 cm. above the level of the third rib. The veins over the right shoulder and the pectoral region had become very prominent and showed appreciable upward and mediad blood flow. One week after discharge the venous pressure in the right arm fell to 15 cm. of physiologic salt solution.

The patient was discharged after one week of hospital care. He was examined at intervals during the succeeding six months. Slight swelling in the arm continued for about three months, and thereafter was noted only after activity. The tender cord in the region of the brachial and axillary veins had disappeared.

This case may be classified as Type 3. The physical work involved in throwing the baseball was vigorous and unusual. The striking feature in this case was the long delay between the onset of the pain which probably represented the initial trauma and the occurrence of the thrombosis as a sequel to the secondary trauma of the tennis game. This patient had increased venous pressure and arterial blood pressure in the affected extremity. His partial clinical recovery was prompt.

CASE 2.—(Figs. 3 and 4). S. P. M., a woman, 62 years of age, had had chronic paranasal sinusitis, emphysema, and bronchiectasis, the latter chiefly in the left lower lobe, for at least six years prior to observation in the Out-Patient Department of the University of California Hospital on December 31, 1935. A left-sided phrenicectomy had been done for relief of the last mentioned condition three years earlier. The patient had marked kyphosis, arthritis of the thoracic spine, and anterior protuberance of the upper portion of the sternum. The clavicles were directed upward and posteriorly in her natural erect posture. Two weeks previously, after more than ordinary housework, cyanosis and swelling of the entire left arm and hand, without pain, had set in; this condition had continued unaltered to the time of entry into the hospital.

The left arm and hand were of a mottled, bluish color, and the superficial veins in the extremity and over the shoulder and left pectoral region were distended. No thrombotic vein was palpated, but there was tenderness in the axilla. The blood pressure was the same in both arms, namely, 150/80. After resting the extremity for one week, the swelling and cyanosis disappeared. A year later there was no apparent difference in the two arms, although the left arm ached occasionally on motion.

This case may be classified as Type 1 or Type 3.

CASE 3.—E. M., 37 years of age, was a slender, well-developed man with a somewhat broad and deep upper chest; his clavicles were directed slightly upward and posteriorly in his normal posture. He was a dishwasher in a restaurant, and constantly used the left hand more than the right. Three months, and again one and one-half weeks, prior to his entry at the University of California Hospital on December 5, 1934, he had had attacks of pleurisy on the left and right sides successively,

from which he had recovered completely. No active tuberculosis had been found. One week prior to entry, while lifting the cover of the dishwasher with both hands after washing dishes, he noticed that the entire left arm was purplish in color and felt tense, and that the superficial veins were distended. These changes were less



Fig. 3.

Fig. 3.—Infrared photograph of patient in Case 2, illustrating the deep upper chest with posteriorly directed axillaries and the distended veins of the left arm, shoulder, and pectoral region. (Reproduced from Mediosternal Tributaries to Harold Brann.)
 Fig. 1.—Roentgenogram of the upper chest and shoulder in Case 2. The high fluorescent position of the upper ribs and the posteriorly directed axillaries may be observed. (Reproduced from Mediosternal Tributaries to Harold Brann.)
 Fig. 2.

marked when he was in a reclining position or when he elevated the arm. He continued work and the arm became increasingly swollen and cyanotic. At the time of his hospitalization the engorged veins extended from the extremity over the shoulder to the margin of the left sternomastoid muscle and over the upper pectoral region to the sternal border. The left infraclavicular and scapular regions were also slightly indurated. No thrombosed veins were felt in the left arm or axilla. The blood pressure was not recorded. There was only slight improvement with rest during the sixteen days of hospitalization. The patient was not followed thereafter.

This case may be classified as Type 2, for the left arm and shoulder were used vigorously in dishwashing.

CASE 4.—M. M., a housewife, 48 years of age, entered the University of California Hospital July 7, 1919, with complaints referable to generalized arthritis and pes planus. She was deep-chested. Four years prior to admission, after no unusual effort other than routine housework, she had observed swelling and cyanosis of the right hand and forearm which had extended rapidly to the entire right arm and shoulder. A tender lump had been noted in the right axilla. A diagnosis of a thrombosed vein in the axilla had been made. The swelling had receded gradually over a period of four months and had not recurred. She had had no pain. At the time of her hospital entry in 1919, the right arm was slightly larger than the left and the superficial veins were more distended, not only over the arm but also over the upper right anterior portion of the chest. The blood pressure was not recorded.

This lesion may be classified as Type 1. No obvious traumatic activity occurred. The persistent recurrence for a period of four years of the signs and symptoms of thrombosis after work involving the right arm was an interesting feature of this case.

CASE 5.—R. P., a carpenter, 22 years of age, a broad, deep-chested man with good muscular development, entered the University of California Hospital March 14, 1916, after intense physical activity (sawing, planing, and lifting wood). On March 12, he noted swelling of the entire right arm from the hand to the shoulder. When he resumed work on March 13, the arm became blue and painful and the superficial veins became increasingly distended. Upon pressure over the axilla, pain radiated down the medial surface of the arm.

Examination revealed that the right arm was mottled, reddish-blue in color, swollen and indurated, and the superficial veins and venules in arm, axilla, shoulder, and pectoral region were distended. A tender cord was palpated in the region of the brachial and axillary veins. Six days later the swelling had subsided, and only a trace of the induration was noted on discharge ten days after admission.

This case, precipitated by vigorous use of the right arm in carpentry, may be classified as Type 3.

The hypotheses concerning the pathogenesis of this condition may be summarized as follows:

1. Von Schroetter⁵ stated that trauma of the wall of the vessel was caused by stretching the subclavian and axillary veins and by compression, but he did not give a precise definition of the forces involved.

2. Willan²² believed that the compressing force was between the medial border of the pectoralis minor muscle and the first rib, and that stretching of the vein occurred.

3. Gould and Patey³ believed that the pressure of the subclavius muscle on the vein lying on the first rib was the most important traumatic agent. Others, including Aschoff,⁶ Löhr,³⁴ and later investigators tenta-

tively assumed that the subclavius muscle or the clavicle and the first rib were the important compressing agents.

4. Cadenat³⁵ and Lahaussais³⁶ presented the theory that distention of the subclavian vein from increased respiratory effort preceded the traumatic compression and contributed to it. This conception was accepted by Lowenstein,³⁷ Veal and McFetridge,³⁸ and others.

5. Cottalorda,¹⁷ Löhr,³⁴ and, more recently, Hammann² suggested that primary or secondary spasm of the vein was induced by the trauma and that thrombosis was not necessary for venous obstruction. Occasional operations which failed to reveal a thrombus in the vein confirmed this hypothesis.³⁹

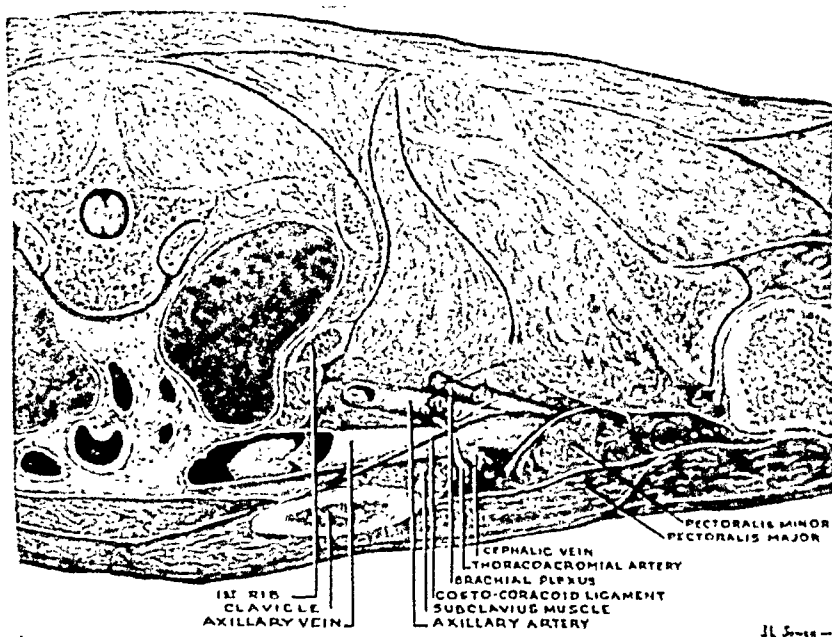


Fig. 5.—Anatomic relationships of the axillary vein, illustrating the costocoracoid ligament which crosses that vessel. (Reproduced from Lowenstein.³⁷)

6. Lowenstein³⁷ demonstrated the anatomic relationships of the costocoracoid ligament and presented the hypothesis that compression of the axillary vein was produced by that ligament at a point 35 to 45 mm. distal to the crossing by the vein of the highest point on the first rib (Fig. 5).

7. Veal and McFetridge³⁸ stated that the compression of the vein which is responsible for the thrombosis occurred in the axilla between the abducted head of the humerus and the subclavius muscle. They demonstrated this hypothesis by diodrast visualization of the veins (Figs. 6 and 7).

8. Lastly, Benda,⁴⁰ Moure and Martin,³⁹ and others believed that a hematoma in the axillary region was often responsible for the compression of the vein.

In 1940, Sampson, Saunders, and Capp⁴¹ presented the hypothesis that partial compression of the subclavian vein by the clavicle or subclavius muscle and the first rib is not an uncommon occurrence, and is responsible for the distention of the superficial veins of the anterior shoulder and pectoral region that is frequently seen. They stated that persons with high, horizontally curving first ribs and upwardly and backwardly directed clavicles tend to show this clinical picture because of compression of the subclavian vein in the first third of its course (Fig. 8). Collateral circulation, which results from the obstruction of the main

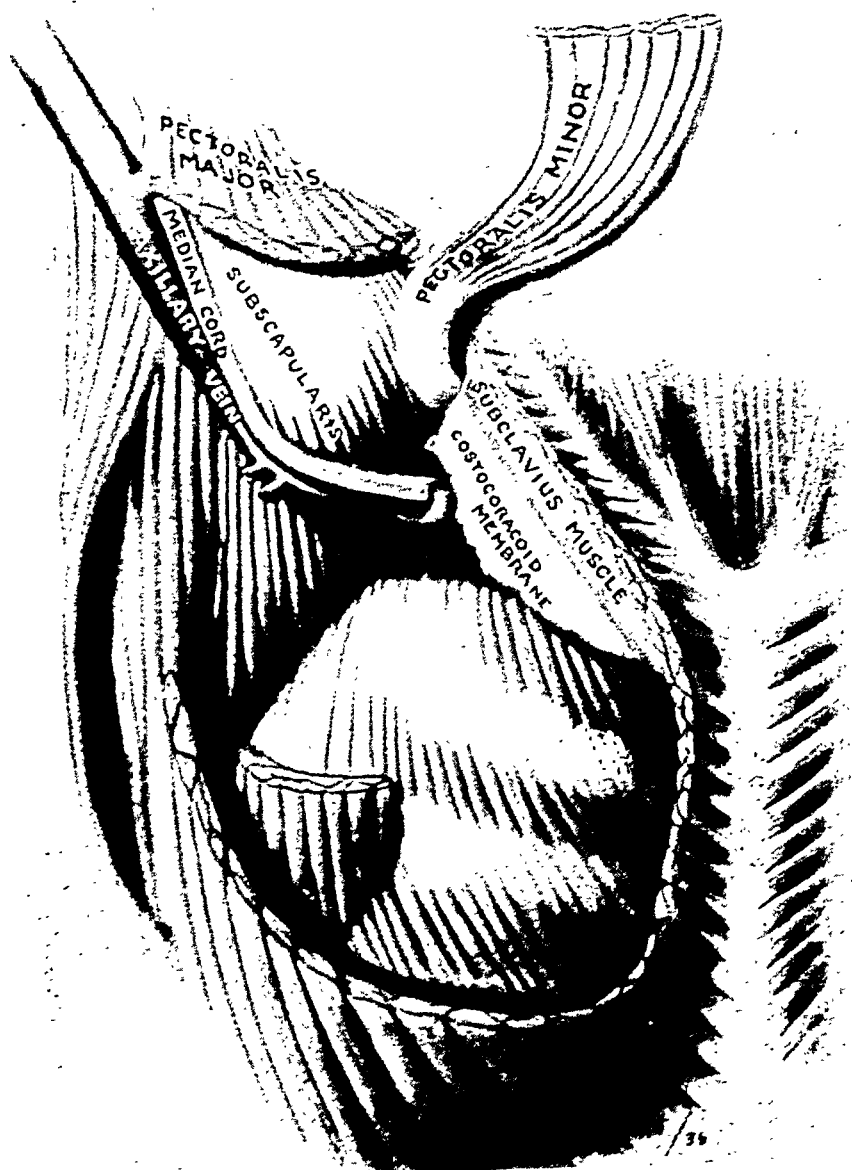


Fig. 6.—Drawing illustrating anatomic relations of parts of the axillary region when the arm is in a position of hyperabduction and external rotation. Note the constriction of the axillary vein against the subscapularis muscle and the stretching of the vein just proximal to the point of constriction. (Reproduced from Veal and McFetridge.²)

deep channels, increases the pressure in, and the size of, the superficial veins. Persons who tend to have these prominent veins usually have broad chests and good postures, with shoulders naturally held back. Cases were presented to demonstrate that obstruction of the subclavian vein is increased by a voluntary backward thrust of the shoulder girdle without elevation or abduction of the arms (Fig. 9). Thus, those efforts or postures that produce backward and upward (posterior and cephalad) motion of the clavicles tend to obstruct the blood flow in the subclavian vein even if the force of the motion is small and is unassociated with abduction of the arms. Consequently, spontaneous thrombosis of the sub-



Fig. 7.—Roentgenogram showing point of constriction of the axillary vein below the head of the humerus against the subscapularis muscle in a position of hyperabduction and external rotation. (Reproduced from Veal and McFetridge.³³)

clavian vein may occur as a result of the efforts classified as Types 3 and 4, such as holding the arms over the head to clean a ceiling.

Many investigators have stated previously that the zone of compression of the subclavian vein may be between the clavicle and the first rib, but they have not specifically defined the site or the agencies responsible for the compression. However, Lowenstein³⁷ and Veal and McFetridge³⁸ located the compressed segment of the vein lateral to the zone designated by Sampson, Saunders, and Capp.⁴¹ In Fig. 7, from Veal and McFetridge, the radiopaque material does not reveal the subclavian vein proximal to the axilla. Although a compression of the vein in the axilla is demonstrated, a more proximal zone of compression may also have been present without being shown in the illustration.

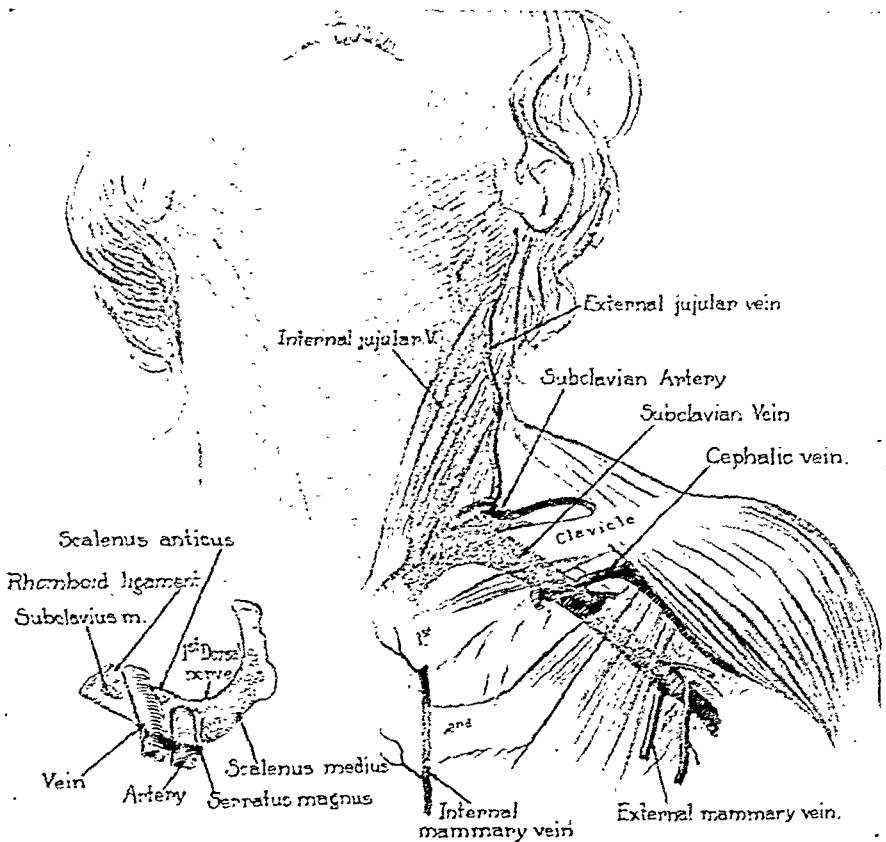


Fig. 8.—Anatomic relationships of the subclavian vein, illustrating its crossing the first rib under the subclavius muscle and clavicle in a narrow triangular space medial to the scalenus anticus muscle. Elevation of the clavicle tends to obliterate this space. (Reproduced from Sampson, Saunders, and Capp.⁴¹)

The mechanism and the zone of compression are well illustrated in a case of Robb and Steinberg.⁴² During a diodrast injection for visualization of the heart, the patient's arm was extended over his head. The radiopaque blood was held in the vein distal to the point of crossing, and, after nine seconds, began to flow partially past an obstruction at that point. Roentgenograms taken prior to the time of release of the obstruction confirmed this observation, and another, taken shortly after

the partial return of flow through the subclavian vein, clearly showed that the area of compression was immediately proximal to the crossing of the first rib by the vein (Fig. 10). The patient had an acute thrombosis of the subclavian and axillary veins as a sequel to this incident. This case illustrates a double cause for the local thrombophlebitis, namely, compression which slowed the blood flow, and an irritant, the diodrast. A similar case was that of a girl, thirteen years of age, on whom diodrast

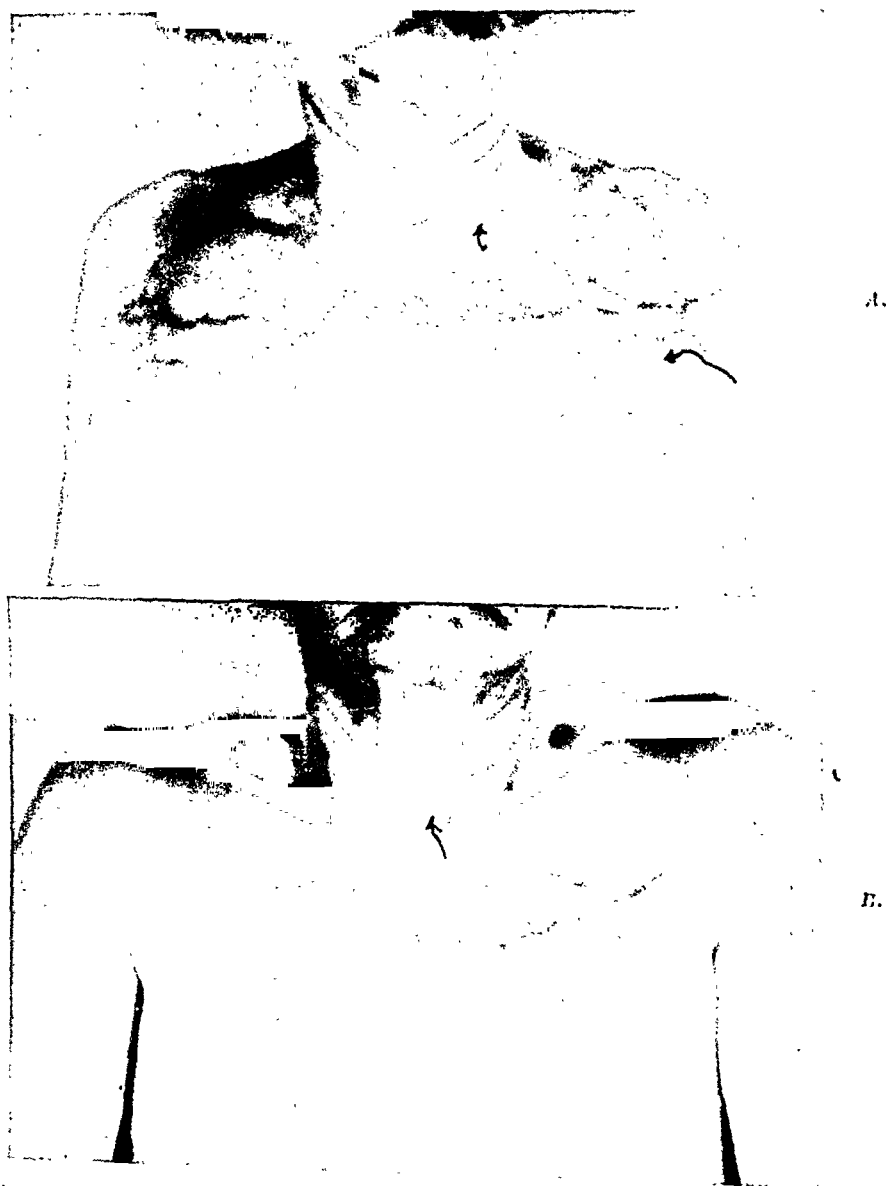


Fig. 9.—Development of prominent collateral veins in a case of chronic compression of the subclavian veins. The patient had a broad, deep chest and "good" posture with posteriorly directed clavicles.

A represents the increased distention of the superficial chest veins when the shoulders are held backward; B shows collapse of these veins when the shoulders are held forward. These changes occur with change of position of the shoulder girdle without abduction or elevation of the arms. (Reproduced from Sampson, Saunders and Capp.⁴¹)

visualization studies were made for diagnosis of a congenital heart lesion. No apparent defects were noted in the peripheral arteries or veins. A roentgenogram taken approximately eight seconds after the injection of diodrast into the median basilic vein, with the arm extended over the head, showed that part of the radiopaque blood had flowed into the superior vena cava, but much of it was held in the subclavian vein distal to the point of apparent obstruction which was immediately proximal to the crossing of the first rib (Fig. 11). A roentgenogram taken approximately three seconds later showed the blood again flowing past the obstruction, and an angulation of the subclavian vein as it crossed under the clavicle into the innominate vein. The zone of compression was shown by narrowing, transparency, and what seemed to be longitudinal



Fig. 10.—Roentgenogram in case of Robb and Steinberg, illustrating the definite indentation of the subclavian vein as it crosses the superior margin of the first rib. The clear area between the clavicle and the diodrast-filled subclavian vein probably represents the space occupied by the subclavius muscle. (Reproduced from Sampson, Saunders, and Capp.⁴¹)

folding of the vein (Fig. 12). These two cases confirm the hypothesis offered in this paper, rather than the hypotheses offered by Lowenstein and Veal and McFetridge.

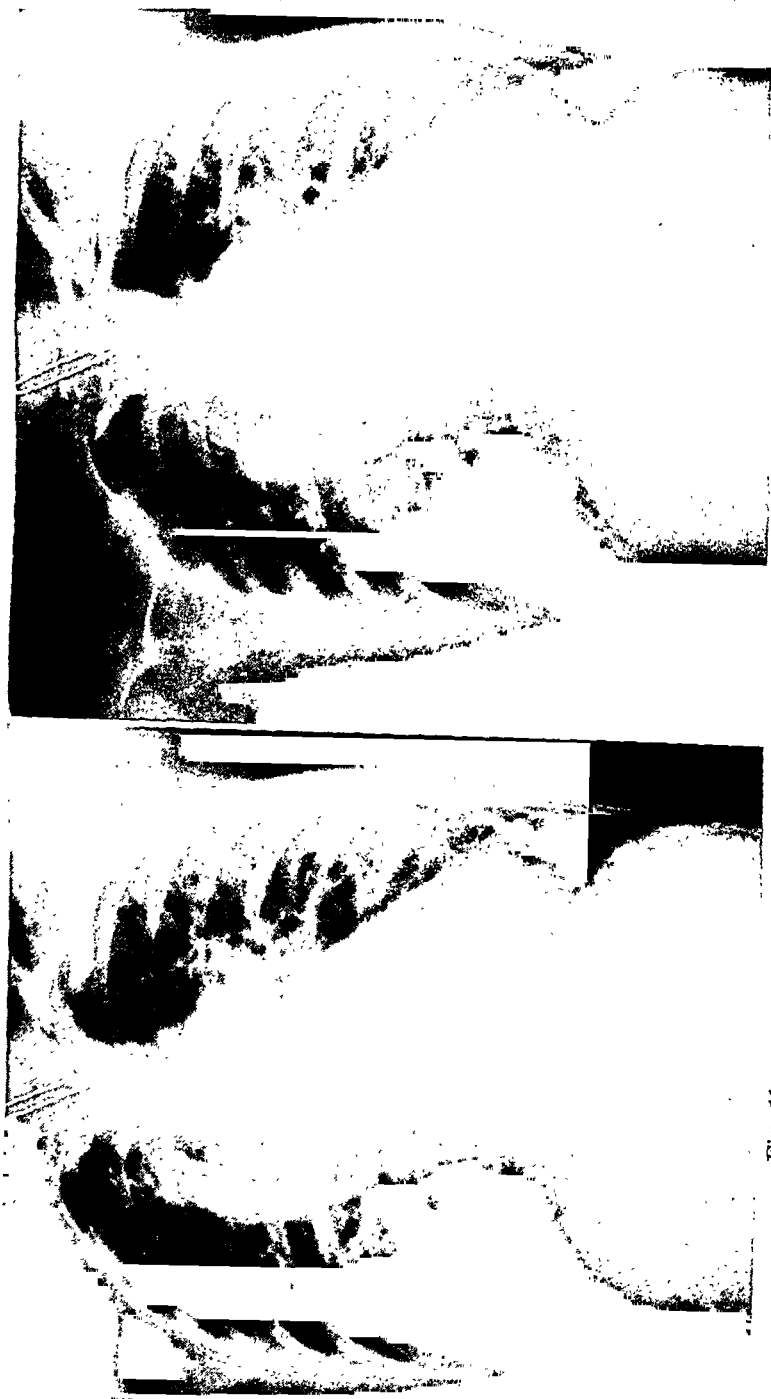


Fig. 11.

Fig. 11.—Roentgenogram taken 8 seconds after injection of diodrast, showing point of obstruction in the subclavian vein immediately proximal to its crossing of the first rib. (Reproduced from *Medico-Surgical Tributes to Harold Brunn*.)

Fig. 12.

Fig. 12.—Roentgenogram taken approximately eleven seconds after injection of diodrast. The blood is again flowing past the obstruction. An angulation is shown in the subclavian vein as it crosses under the clavicle into the innominate vein. (Reproduced from *Medico-Surgical Tributes to Harold Brunn*.)

It is the additional intention to present in this paper the possibility that the disease in all four classifications of activity may have resulted from a predisposing anatomic configuration of the clavicles and first ribs. The hypertrophy of the subclavius muscles that should occur in muscular, athletic men and women may be a contributing factor. In the numerous cases reported in the literature, no data are given to confirm this hypothesis. But in Cases 1 and 2 the characteristic rib and clavicle relations were demonstrated by physical examination and roentgenographic studies (Figs. 1, 2, 3, and 4). The routine method of taking roentgenograms of the chest was used in these two cases; this consists of having the patient extend his arms forward around the cassette, which tends to throw the shoulders forward. Thus, the roentgenograms show the clavicles in a lower position than normal, as illustrated in the photographs. Studies of chest and clavicle positions were not made in Cases 3, 4, and 5.

It is conceded that with sufficient trauma or other anatomic variation, thrombosis may occur without the causative factors presented herein.

CONCLUSIONS

1. Five cases of primary thrombosis of the axillary vein have been presented.

2. The clinical picture has been described, and these cases, as well as cases from the literature, have been classified according to types of physical activity which produce the lesions.

3. Compression of the subclavian vein, resulting in thrombosis, often may be caused by a posterior and cephalad rotation of the clavicle that narrows the space between the subclavius muscle and the superior margin of the inner third of the first rib through which the vein passes. This position of the clavicles may result from upward or backward motion of the shoulder girdle without abduction of the arm.

4. The hypothesis is presented that bodily build and posture, associated with broad, horizontally curving first ribs and posteriorly directed clavicles, predisposes to this condition, as well as to chronic compression of the subclavian vein.

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RATE OF PERIPHERAL BLOOD FLOW IN THE PRESENCE OF EDEMA

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THE effect of edema upon the rate of blood flow in the extremities has been studied by a number of investigators. Harrison and Pilcher¹ found that edema of the leg, whether caused by cardiac disease or other conditions, was accompanied by a high venous oxygen content and a low femoral arteriovenous oxygen difference. They considered their results to indicate that there is a greatly reduced consumption of oxygen by edematous tissues, and, further, that the rate of blood flow through these tissues is increased. Weiss and Ellis,² however, using the same method, were unable to confirm the results obtained by these workers. They observed no relationship between the degree of edema and the arteriovenous oxygen difference. Further, in the same subject the readings for the edematous lower extremity were nearly the same as those for the nonedematous upper extremity. They, therefore, interpreted their data to indicate that there is no increase in blood flow in the edematous leg.

Since the procedure used in the above investigations gave only an indirect measure of the rate of blood flow, and since the results obtained by the two groups of workers were contradictory, it was considered worthwhile to reinvestigate the subject, using the venous occlusion plethysmographic method.

METHOD

The study was performed upon seven patients with edema of one extremity, upon five patients with edema of both lower extremities unassociated with organic cardiac disease, and upon seven patients with edema of both lower extremities caused by chronic congestive heart failure. Blood flow readings, in c.c. per minute per 100 c.c. of limb volume, were obtained separately upon the hand, forearm, or leg, according to the technique previously described.³ The room temperature was maintained between 25° and 27° C., and the bath temperature at 32° C. In the case of the forearm, the cuff utilized in applying the collecting pressure was wrapped around the arm just above the elbow, and, in the case of the leg, around the thigh just above the knee. With respect to the hand, the pressure was applied to the forearm, about three inches from the wrist. These steps were taken in order to minimize the possibility that, during a blood flow reading, edema fluid might be expressed from under the cuff into the portion of the limb in the plethysmograph, and thus produce an artifact. The only objection to this procedure, as compared with placing

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the cuff around the extremity immediately proximal to its insertion into the machine, is that the readings might possibly be somewhat smaller than the true blood flow value. In addition, when studying the forearm and leg, special precautions were taken with respect to the cuffs at the wrist and ankle, which were utilized in preventing arterial inflow into, and venous return from, the hand and foot, respectively, during a blood flow measurement. Since there was a possibility that the application of the arterial occlusion pressure might result in a movement of edema fluid from the wrist or ankle into the lower portion of the segment of the extremity under study, and since this might continue for some time after the step was performed, it was considered advisable to apply and maintain the pressure for at least three or four minutes before obtaining a blood flow reading.

For the group with edema of only one extremity, the results obtained on the contralateral normal limb were used as a control. In the cases of edema of both lower extremities, either because of congestive heart failure or other conditions, the data obtained on a series of ninety normal subjects, previously reported,⁴ were used for a similar purpose.

Besides blood flow measurements, blood pressure, circulation time,* and venous pressure studies were made upon many of the patients.

RESULTS

The readings obtained in the first group of subjects, in which edema of only one extremity was present, are shown in Table I. In the case of *D. R.*, the left upper extremity was moderately edematous as a result of pressure of metastatic carcinoma on axillary structures; the rate of blood flow in the edematous hand was significantly greater than on the contralateral control side. Subject *B. B.* presented a brawny type of edema of the left hand caused by breast neoplasm and lymphatic involvement, and again the flow was greater than on the normal side, although the difference was not as marked as in *D. R.* In two subjects, edema of one hand occurred in the period immediately after the onset of hemiplegia. As controls for these patients, blood flow readings were obtained in a group of ten subjects with a similar type of hemiplegia, but without edema. There was no significant difference between the rate of blood flow in the paralyzed hand and the normal hand in this group. With respect to the two subjects with edema, in one (*E. D.*) the blood flow in the edematous hand was definitely better than that in the contralateral side, whereas, in the other (*A. A.*), the figures were approximately the same for both the edematous and normal hand.

Of the two subjects whose forearms were studied, in one (*E. K.*) there was marked edema of the left upper extremity, but the right side was normal. This patient had definite signs of congestive heart failure, as indicated by the presence of edema of both the lower extremities, a circulation time of twenty-seven seconds, and a venous pressure (right arm) of 27.6 cm. of water. There was no explanation for the edema of the left upper extremity, but it was not regarded as a manifestation of heart failure because of the fact that it involved only one of the upper

*Circulation time measurements were performed with "Decholin," kindly furnished by Riedel-de Haen, Inc.

TABLE I

RATE OF BLOOD FLOW IN EDEMATOUS EXTREMITIES, COMPARED WITH CONTRALATERAL CONTROL SIDE

SUBJECT	INVOLVED SIDE			CONTROL SIDE			REMARKS
	EXTREM.	VOL.	B. F.	EXTREM.	VOL.	B. F.	
D. R.	L. hand		11.6	R. hand		6.2	
B. B.	L. hand	460	5.1	R. hand	325	3.3	
E. D.	R. hand	630	16.2	L. hand	395	4.9	R. Arm L. Arm Ven. pres. 10 cm. 11 cm. B. P. 172/110 168/112
A. A.	R. hand	486	4.9	L. hand	300	5.4	
E. K.	L. forearm	740	4.9	R. forearm	485	1.8	L. Arm R. Arm B. P. 142/70 140/66
D. J.	L. forearm	740	1.7	R. forearm	420	2.0	L. Arm R. Arm B. P. 142/98 150/100
W. H.	R. leg		4.0	L. leg		2.6	

B. F.—Rate of blood flow in c.c. per minute per 100 c.c. of limb volume.

Vol.—Volume of extremity in plethysmograph, only included in table in those instances in which the same length of involved and normal extremities was studied.

limbs. In any event, the rate of blood flow in the edematous forearm was definitely greater than that of the normal side. In the other subject (D. J.), brawny edema occurred in the left forearm after radical breast amputation for carcinoma; there was no significant difference in blood flow between the involved and control sides. In the last subject of this series (W. H.), the right lower extremity was moderately edematous as a result of metastasis from a prostatic carcinoma; the blood flow in the affected leg was definitely greater than that in the normal side.

In the second group of patients, edema of both lower extremities, unassociated with congestive heart failure, was present; the arm-to-tongue circulation time in each instance was within the range for normal subjects (Table II). With respect to M. W., no explanation could be offered for the moderate degree of edema of both legs, except that there was a history of thrombophlebitis twenty years previously. Both pigmentation and eczema were present in the skin, possibly as a result of venous and lymphatic involvement. In the case of E. E. and H. E., there were no signs of dietary deficiency, but both subjects admitted having imbibed large quantities of beer over a long period of time. H. W. showed all the classical signs of a nephrotic syndrome, and J. P. had a history of soft tissue abscesses for the preceding thirteen years, associated with chronic brucellosis, and was now suffering from amyloid disease.

In respect to the rate of blood flow in the edematous lower extremities in this series, examination of Table II reveals that in all instances the figures were either somewhat or definitely beyond the average range of 1.4 c.c. per minute per 100 c.c. of limb volume, $\sigma -0.5$,* observed in the control subjects.

*Standard deviation.

TABLE II
RATE OF BLOOD FLOW IN EDEMATOUS LEGS, UNASSOCIATED WITH CONGESTIVE HEART FAILURE

SUBJECT	DISEASE	BLOOD FLOW IN LEG	CIRCULATION TIME IN SEC.	BLOOD PRESSURE	REMARKS
M. W.	?	2.5	12	128/82	
E. E.	Cirrhosis of liver	2.2	12	154/56	
H. E.	Cirrhosis of liver	2.3	18		
H. W.	Nephrosis	R. 2.7 L. 3.2	12	126/74	Ven. pres. (fem. vein), 9 cm. H ₂ O; plasma cholesterol, 283 mg. %; serum protein, 4.0 mg. %; A:G ratio, 0.9. P.S.P., 75% excretion in 1 hr.
J. P.	Amyloidosis	2.4		132/70	Positive Congo red test. Albuminuria, casts. No hematuria.

Blood flow in c.c. per min. per 100 c.c. of limb volume.

In the third group of patients, edema of both lower extremities was associated with definite signs of chronic congestive heart failure; the arm-to-tongue circulation time was significantly increased in each instance. In two of the eight patients (H. N. and M. O.), auricular fibrillation had replaced normal sinus rhythm. Subject P. C. had mitral stenosis and congestive heart failure, and was also in the eighth lunar month of pregnancy.

TABLE III
RATE OF BLOOD FLOW IN THE EDEMATOUS LEG AND NONEDEMATOUS FOREARM OF PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

SUBJECT	BLOOD FLOW		CIRCULATION TIME IN SEC.	REMARKS
	LEG WITH EDEMA	FOREARM		
H. N.	1.1			Auricular fibrillation
A. S.	1.9		23	
P. C.	1.4	3.4	29	
J. B.	2.5	1.3	47	Eighth lunar month of pregnancy 2+ edema of leg No edema of leg
	1.3	1.1	39	
M. C.	1.7	1.2	22	
P. M.	1.2	2.0		
M. O.	1.4	1.9		Auricular fibrillation

Blood flow in c.c. per min. per 100 c.c. of limb volume.

As a whole, the blood flow readings obtained in the edematous legs in these patients (Table III) were smaller than those observed in the second group, in which the edema was of noncardiac origin. All the figures for the cardiac patients, however, fell within the range of the results obtained in the normal series (1.4 c.c., σ -0.5). The case of J. B. is of special interest, for measurements were obtained when the edema was present and again after it had disappeared as a result of

treatment. Examination of Table III reveals that the second reading in the leg was definitely less than the first; the blood flow in the non-edematous forearm was the same on the two occasions. With the exception of P. C., the measurements on the forearm in all the subjects with chronic congestive heart failure were within the normal range of 1.8 c.e. per minute per 100 c.e. of limb volume, $\sigma -0.7$. As previously stated, subject P. C. was in the eighth lunar month, and the increased circulation may have been caused by this fact, for it has been shown that, in some subjects, an augmentation in forearm blood flow may occur during the latter two trimesters of gestation.⁵

DISCUSSION

When the venous occlusion plethysmographic method is utilized in the study of the rate of peripheral blood flow in edematous extremities, certain objections can theoretically be raised. The first possibility, namely, that edema fluid might be forced into the segment of the limb under study by the application of either the venous or arterial occlusion pressure, has been adequately dealt with, we feel, by our method of placing the blood pressure cuffs. Further, any sudden increase in limb volume produced in this way could readily be identified on the record, for it would produce an abrupt change in the slope of the curve. All blood flow records which showed a sudden initial rise and then a more gradual ascent were either discarded or only the latter portion of the curve was utilized in the measurement of rate of blood flow. Another possible objection is that the presence of edema fluid might mechanically slow the rate at which the limb volume increases on application of the collecting pressure. Since the accumulation of blood takes place for the most part in the thin-walled veins, it is conceivable that edema fluid might act to prevent the rapid filling of this system and thus cause some obstruction to the continued flow of blood into the limb. This might result in obtaining a rate of blood flow which would be smaller, but certainly not larger, than that actually present.

Another factor which must be taken into consideration when comparing the peripheral circulation in an edematous extremity with that in a nonedematous one is the fact that in each case the reading is expressed as the number of c.e. of blood flow per minute per 100 c.e. of limb volume. The volume of the portion of the extremity in the plethysmograph is obtained by water displacement, and hence, in the case of the edematous limb, a considerable amount of edema fluid is included in this figure. This is clearly shown (Table I) in those instances in which the same length segment of edematous and normal extremities was included in the plethysmographs. In each case the volume of the involved limb was greater than that of the contralateral control side. If the figures for limb volume could be corrected for the inclusion of edema fluid, obviously the blood flow readings for the edematous extremities in all of our cases would become greater. It is a good possibility that the values

for the involved extremity in the case of A. A. and D. J. would, under these circumstances, be greater than those for the normal side.

Since there is a definite spread of blood flow readings in any series of normal subjects, there may be an objection to comparing the average for the group with the results obtained in a small number of patients. We do not consider this to apply, however, to the observations on the subjects with bilateral edema unassociated with chronic congestive heart failure, for, in every instance, the readings were beyond the upper range of the normal series. Besides, as in the case of the first group, correction for the factor of edema fluid in the volume of the limb would have further increased the magnitude of the blood flow readings in the edematous extremities. Whether this factor alone would have been sufficient to raise the average rate of local blood flow in the involved limb in congestive heart failure to a level above normal is difficult to state.

It would seem, then, that the peripheral circulation in an edematous extremity, unassociated with organic involvement of the heart, is, for the most part, increased, and certainly not decreased. The explanation for this observation is not clear. An elevated venous pressure is not, by itself, an important factor, for, in a number of our cases, the venous pressure was normal, and, nevertheless, the blood flow was increased. Further, it has been observed that, in pregnancy, in which a high femoral venous pressure is produced mechanically by the enlarging uterus,⁴ the peripheral circulation through the leg remains within normal limits in at least the last two trimesters,⁵ a period during which the venous pressure is the highest. It is generally accepted that edema fluid interferes with the normal interchange of oxygen between the blood stream and the tissues and with the removal of the various end products of metabolism. It is conceivable, then, that the anoxia resulting therefrom or the accumulation of vasodilator substances locally, or both of these factors, might be effective in producing arteriolar vasodilatation and an increase in blood flow to the part.

SUMMARY AND CONCLUSION

The peripheral circulation was studied in a series of nineteen patients who had edema in either a single upper or lower extremity or in both lower limbs. The venous occlusion plethysmographic method was used to ascertain the rate of blood flow separately in the hand, forearm, and leg.

It was found that the peripheral circulation in edematous extremities, unassociated with organic heart disease, was, for the most part, increased, and certainly not decreased. In respect to the patients with chronic congestive heart failure, the blood flow readings on the edematous limbs fell within the range of those obtained on normal subjects.

The possible circulatory mechanisms which are responsible for the changes in peripheral blood flow in edema are considered.

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INVESTIGATIONS CONCERNING VITAL CAPACITY

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SINCE having been established nearly a century ago¹ as a quantitative measure of respiration, measurement of the vital capacity has found universal clinical application because of the ease with which it is done and its utility in clinical orientation, especially with regard to heart disease. Vital capacity measures the extensibility of the lungs, and is inversely proportional to the degree of engorgement of the lungs. Measurements of vital capacity enable us to estimate quantitatively the degree of pulmonary congestion, and thus, together with the other hemodynamic data, affords a clearer view of circulatory conditions. Its measurement is therefore considered indispensable in cases of heart disease.

The present study treats of some new aspects of spirometric research which have, in my experience, not only theoretical, but practical value.

According to the classical definition, the vital capacity is the volume of air, in cubic centimeters, which can be expelled by maximum expiration after maximum inspiration. For the actual study, the minimum duration of the expiration that represents the vital capacity was ascertained. In this way, two values were obtained: the vital capacity and the minimum duration of the forced expiration. Dividing the vital capacity by the number of seconds thus ascertained, we arrive at the value for the velocity of spirometric respiration. By this term we understand that quantity of air which corresponds to the average velocity of the quickest expiration.

In order to characterize more exactly the respiratory function in relation to spirometric determination of the maximum volume, I looked for, and found, by means of a manometer, another respiratory factor: the expiratory pressure. Following the definition of vital capacity, I ascertained the maximum pressure which the subject will generate when exhaling into a manometer after having inhaled as deeply as possible. The altitude of the mercury column represents the maximum expiratory pressure. Thus the maximum volume and pressure during maximum inspiration and expiration were ascertained.

METHOD

The vital capacity was measured with Barnes' dry spirometer, with the patient standing. At least two measurements were made, and the larger or largest was taken. After a five minutes' rest, the minimum duration of maximum expiration was measured in the following way: The subject, who has been instructed, after comfortably completing the deep inspiration, exhales as rapidly as possible, and care is taken that, during the violent expiration, no air escapes at the sides of the

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mouthpiece. The physician, chronometer in hand, observes attentively the index tube of the spirometer. He takes note of the instant when the tube indicates the entrance of the air in the spirometer, and stops the chronometer when the upward movement of the index tube has reached its end. In general, increasing the velocity of expiration does not depress the numerical value of the vital capacity. The differences between the spirometric quantities, as measured when taking into account the time factor and measured without doing so, must not exceed 100 or 200 c.c. If this should not be the case, despite a reasonable rest, the measurements must be repeated.

In any case, two measurements are made. To ascertain the velocity of the spirometric expiration, the one is utilized that takes the least amount of time, the respiratory volumes being equal, or the one that exhibits, for the vital capacity, the value nearest the one previously established.

The expiratory pressure was measured with the Baumanometer (portable or wall model) in the following way: The cuff connection of the apparatus was joined to a rubber tube 50 cm. long, identical with that used in the spirometer. The subject was instructed to inhale as deeply as possible, and then to exhale into the tube of the manometer violently, so that the mercury column of the apparatus would rise as far as possible. The subjects were standing during this procedure. Although this has been done on hundreds of patients, and marked elevations in the intrapulmonary pressure have been observed, no accident whatever has happened, either to healthy or ill persons; this is in contradistinction to cases in which Bürger's⁴ test was applied. As to the usual complaint about congestion in the head, felt in different degrees from a slight ache to giddiness, it can be stated that these symptoms will completely disappear in a few minutes.

RESULTS

Healthy Persons (Table I).—In a group of thirty healthy persons whose ages varied between 15 and 54 years, the results were as follows: The average vital capacity was 4600 c.c., with variations between 5500 and 4000 c.c., which figures, although they were not related to the surface area of the body, are normal. The minimum time for exhaling the vital capacity volume was, on an average, 3.4 seconds, with a range from 4.2 to 2.9 seconds. The velocity of spirometric respiration was, on the average, 1340 c.c., and individual values varied between 1660 and 1110 c.c. The average maximum expiratory pressure was 119 mm. Hg, and the range was from 180 to 86 mm.

The possibility of a correlation between the fundamental respiratory factors led to an inquiry into the behavior of the vital capacity in relation to the expiratory pressure, using correlation indexes. Since the correlation index showed variations between 59.5 and 30.4, i.e., a difference of 100 per cent, it became evident that there was no intimate relation between the vital capacity and the expiratory pressure. These two factors are independent of each other. It is true that in cases of large vital capacity the expiratory pressure is often high, and vice versa, but there is no constant relation. On the other hand, the velocity of spirometric respiration does exhibit a rather constant correlation with the absolute value for the vital capacity, as well as with the expiratory pressure. The correlation index, Vel./V.C. , averaging 0.2, covers variations not exceeding 31 per cent (0.35 to 0.24). Similar constancy pre-

TABLE I
NORMAL PERSONS

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. HG)	V.C.	VEL.	VEL.
						P.	V.C.	P.
1	29	5500	3.9	1400	138	39.3	0.25	8.8
2	25	5500	3.7	1380	115	47.8	0.25	12.0
3	25	5300	3.6	1470	135	39.2	0.28	10.9
4	39	5200	3.4	1500	170	30.5	0.29	8.8
5	27	5100	3.0	1660	143	35.7	0.33	11.6
6	24	5100	3.0	1660	140	36.4	0.33	11.8
7	54	5000	3.0	1600	180	27.8	0.33	8.8
8	24	5000	3.5	1400	110	45.4	0.28	12.6
9	19	4800	4.0	1200	110	43.6	0.25	10.9
10	34	4800	3.6	1280	90	53.3	0.28	14.2
11	42	4700	3.6	1350	120	39.1	0.28	11.2
12	18	4700	3.5	1200	115	40.8	0.21	10.4
13	42	4700	4.1	1130	95	59.5	0.24	11.8
14	24	4600	4.0	1150	110	41.8	0.25	10.4
15	35	4500	3.0	1480	130	34.6	0.33	11.4
16	38	4500	4.2	1350	95	49.7	0.21	14.2
17	28	4500	3.6	1230	86	52.3	0.28	14.3
18	26	4400	3.4	1400	145	30.4	0.29	9.7
19	36	4400	3.0	1400	128	31.9	0.33	10.1
20	35	4300	3.4	1260	125	34.1	0.29	10.0
21	39	4300	3.6	1140	100	43.0	0.28	11.4
22	41	4300	3.7	1110	100	43.0	0.25	11.1
23	28	4200	3.2	1250	120	33.6	0.31	10.4
24	32	4200	2.9	1410	120	35.0	0.31	11.7
25	28	4200	2.8	1520	120	35.0	0.35	12.6
26	15	4100	3.7	1110	105	39.0	0.27	10.6
27	38	4000	3.1	1280	110	36.3	0.32	11.6
28	37	4000	2.9	1350	110	36.3	0.34	12.2
29	32	4000	3.2	1270	105	38.1	0.31	10.1
30	39	4000	3.1	1290	90	44.4	0.32	14.3
Average	31.8	4600	3.4	1340	119.0			

V. C. = Vital capacity.

Vel. = Velocity.

P. = Pressure.

vails in the index, Vel./Exp. Press., which averages 11.3. It covers a range of 39 per cent, and its extremes are 14.3 and 8.8.

All this can be summed up as follows: The respiratory velocity is a function of the vital capacity as well as of the expiratory pressure, i.e., it is in direct proportion to them.

Clinical Application.—To study the characteristics of diminution of the vital capacity from various causes (cardiac and pulmonary), patients with severe heart failure and others with bronchial asthma and emphysema, without heart failure, were chosen. The ten cardiac patients (Table II) had severe congestive failure, although with different degrees of dyspnea, cyanosis, edema, and engorgement (pulmonary, hepatic). They were, on an average, 50.6 years of age. The vital capacity averaged 1630 c.c., but, in an extreme case, it was reduced to as little as 600 c.c. The velocity of expiration was 3.4 seconds, which was the same as that of the healthy persons; but, since cardiac patients

TABLE II
DECREASED VITAL CAPACITY AS A RESULT OF HEART FAILURE

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. Hg)	CLINICAL DIAGNOSIS
1	40	1300	2.4	540	45	Decomp. aortic insufficiency
2	60	2100	5.0	425	45	Decomp. mitral disease
3	39	1300	3.0	430	50	Decomp. aortic insufficiency
4	64	2200	3.6	610	50	Decomp. arterioscl. heart dis.
5	56	1800	3.9	460	65	Decomp. hypertens. heart dis.
6	44	600	2.0	300	70	Decomp. mitral disease
7	56	2000	3.1	630	70	Decomp. arterioscl. heart dis.
8	42	2100	2.6	800	70	Decomp. hypertens. heart dis.
9	52	2100	5.0	410	70	Decomp. hypertens. heart dis.
10	53	800	2.9	275	70	Decomp. aortic insufficiency
Average	50.6	1630	3.4	488	61	

with congestive failure need the same time as healthy persons to exhale their reduced vital capacity volume, which is only one-third of that of the healthy persons, that value means nearly a tripled duration of expiration, and the fact that the velocity of spirometric expiration averaged 488 c.c. per second is in perfect accord with this.

The most important abnormality was in the expiratory pressure. It was reduced to 45 mm. in the extreme cases, and averaged 61 mm., or half of the normal value. There was no correlation between the vital capacity, rate of expiration, expiratory velocity, and expiratory pressure. Individual factors accounted for the respective values.

TABLE III
DECREASED VITAL CAPACITY CAUSED BY PULMONARY DISEASE

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. Hg)	CLINICAL DIAGNOSIS
1	43	2000	4.0	500	130	Emphysema, chronic bronch.
2	62	1200	3.2	370	125	Emphysema, chronic bronch.
3	47	2200	4.6	480	120	Asthma
4	53	2100	3.1	670	120	Asthma
5	56	1200	3.6	280	115	Asthma
6	60	1000	2.8	350	110	Asthma
7	56	600	6.4	94	100	Emphysema, chronic bronch.
8	45	1100	6.1	180	100	Asthma
9	60	2000	3.7	540	100	Asthma
10	50	2400	3.6	660	100	Emphysema, chronic bronch.
Average	52.6	1580	4.1	412	112	

The ten patients with decreased vital capacity as a result of pulmonary disease (Table III) were nearly of the same age as the cardiac patients, i.e., 52.6 years. They exhibited a still more marked diminution of the vital capacity (average, 1580) but, on the other hand, the expiratory velocity averaged 4.1, which value indicated slower exhalation in accordance with the average value for the velocity of spirometric

respiration, i.e., 412 c.c. per second. With respect to the alterations of vital capacity and duration and velocity of expiration, these patients showed changes similar to (but more marked than) those of the cardiac patients, but the behavior of the expiratory pressure was very different: i.e., it was normal or only slightly reduced (average value, 112mm.).

Combination of the spirometric data with measurements of the respiratory pressure allows us to reach an objective differential diagnosis of the causes of reduced vital capacity, either cardiac or pulmonary. A normal or slightly decreased expiratory pressure indicates a pulmonary origin, whereas a marked diminution of the pressure is characteristic of cardiac disease.

By applying the procedure described above to typical cases of either pulmonary or cardiac disease, it was possible not only to establish the alterations characteristic of either, but also to make an etiopathologic analysis of the intervening factors in cases in which pulmonary and cardiac diseases coexisted.

TABLE IV
MISCELLANEOUS CASES

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. HG)	DIAGNOSIS AND CLINICAL CONDITION
1	28	700	4.0	175	80	Asthma with slight cardiac decompensation
2	58	800	3.0	260	70	Hypertension, chronic bronchitis, slight decompensation
3	69	2100	4.3	490	85	Emphysema, slight decompensation
4	41	3100	3.4	930	115	Bronchial asthma in free interval
5	50	3100	3.1	1000	110	Bronchial asthma in free interval
6	62	1100	3.6	300	85	Emphysema, marked decompensation
7	32	1500	2.6	570	110	Mitral stenosis and insufficiency, decompensated
8	47	4200	3.5	1170	170	Aortic insufficiency, perfectly compensated
9	49	4000	3.4	1170	140	Mitral disease, perfectly compensated
10	15	3700	3.0	1190	110	Aortic insufficiency, perfectly compensated

Table IV gives data on ten complex cases. The first patient suffered from bronchial asthma. He was examined during an attack. This case was characterized by a relatively low expiratory pressure, indicating some kind of heart failure. The patient had a symptom of slight heart failure, namely, fatigability, even apart from the attacks. His heart was slightly enlarged, especially the right auricle and ventricle. T_2 and T_3 of the electrocardiogram were nearly isoelectric, indicating myocardial damage. In short, his disease was mainly pulmonary, without excluding cardiac affection.

Case 2 was similar in every respect.

In Case 3 the patient showed electrocardiographic alterations suggestive of damage of the myocardium, a moderate diminution of the vital capacity, slow expiration, and a moderate decrease in the expiratory pressure, indicating cardiac disease.

In Case 6 the situation was the same, except that the pulmonary factor was more marked.

In Cases 4 and 5 (bronchial asthma, in free interval) there was no heart disease, for the vital capacity was only moderately decreased, the expiratory pressure was normal, and the expiratory velocity was nearly normal.

In Case 7 the patient had a valvular lesion and heart failure, with marked dyspnea and edema, but, as a discordant factor, a normal expiratory pressure. This is certainly not frequent, and must be explained in the following way: The patient, when in a state of perfect compensation, must have had an elevated expiratory pressure. His actual pressure, although apparently relatively normal, was already a reduced pressure which would sink still lower if the heart failure were to continue.

In Cases 9 and 10, the patients were suffering from valvular lesions, but had no heart failure. It is striking that these patients should respond normally, although their expiratory pressures were clearly higher than normal.

TABLE V
PSEUDONORMAL VITAL CAPACITY

NO.	AGE (YR.)	VITAL CAPACITY (C.C.)	EXPIR. TIME (SEC.)	EXPIR. VELOCITY (C.C. PER SEC.)	EXPIR. PRESSURE (MM. HG)	DIAGNOSIS AND CLINICAL CONDITION
1	53	4000	5.9	670	75	Arteriosclerotic heart disease, compensated.
2	65	3700	4.1	900	80	Arteriosclerotic heart disease, slight decompensation.
3	45	3600	4.6	780	60	Aortic insufficiency, myocardial lesion, slight decomp.
4	44	3500	7.5	460	95	Silicosis.
5	50	3100	4.6	750	60	Mitral and aortic insufficiency. Slight decompensation.
6	60	3300	4.9	680	80	Arteriosclerotic heart disease, myocardial damage.
7	42	3300	4.0	820	70	Myocardial degeneration.
8	45	3200	8.4	360	60	Aortic aneurysm, myocardial damage.
9	50	3100	3.6	830	65	Myocardial degeneration.
10	65	3100	5.4	570	80	Hypertension, slight decompensation.

Table V presents data on patients with pseudonormal vital capacity. Although these persons had a normal vital capacity, the symptoms and signs indicated marked pathologic alterations. It is in these cases that the results of the spirometric and clinical examination contradict each other. But, on investigating the respiratory velocity and the expiratory pressure, we find that, behind the normal vital capacity, a pathologic situation is hidden. Thus it is that, by deeper investigation of the respiratory function, we recognize the real situation in cases in which, in spite of the apparently pathologic state, the vital capacity could be classified as normal.

DISCUSSION

In general, the following functional factors determine the numerical value of the vital capacity: (1) the cardiac factor, (2) the pulmonary factor, (3) the muscular factor, and (4) the psychological factor.

The cardiac factor has to do with the blood volume in the lungs. Pulmonary engorgement increases the blood pressure in the pulmonary circulation and, with the help of changes in intrapulmonary gas pressure, biochemical alterations, and alterations in the capillary permeability, produces pulmonary edema and a diminution in the air volume of the lungs.

The pulmonary factor embraces pulmonary elasticity and the amount of functioning alveolar membrane, both of which may be reduced by emphysema or disease of the parenchyma itself.

Although, under normal conditions, expiration is a passive act, forced expiration, or expiration against resistance, is the result of a muscular effort in which all the expiratory muscles, normal and auxiliary, participate. Therefore, the vital capacity may be decreased through muscular insufficiency, although, properly speaking, no abnormalities either of the circulation or of respiration exist. This occurs in cases of Addison's disease, Graves' disease,² and myxedema. The muscular factor also plays an important role in diminution of the vital capacity caused by cardiac disease. Psychic factors, such as will power, spirit of cooperation or competition, or vanity provoked by indifference, may modify the vital capacity.

Although there are abundant physiologic and clinical observations on vital capacity, not many measurements of the pressure generated during forced expiration have been made. On measuring the maximum expiratory pressure in three persons, Senner³ found a range from 50 to 120 mm. Hg, and Bürger⁴ states that the maximum value for healthy persons is about 140 mm. Hg.

My studies indicate that healthy persons can produce, on the average, a pressure of 119 mm.; this implies an ample range of higher values, but a narrow range of lower ones. The pressure during maximum expiration does not depend on the vital capacity, but is related to the

strength of the expiratory muscular apparatus. Henderson,⁸ Eppinger,⁵ and Budelmann⁶ have, by direct measurements, observed the diminution in the tonicity of muscles in cases of cardiac insufficiency. To explain the diminution in vital capacity in cases of infection, Pries⁷ has accepted Eppinger's theory that, in serous inflammation, the cause is an alteration in capillary permeability, which may produce a diminution in the tonicity of the muscular apparatus. The latter is directly responsible for the diminution in the vital capacity. The decrease in the expiratory pressure in cases of cardiac insufficiency illustrates again the often observed fact that there is diminished tonicity of the muscles in such cases. In absolute conformity with clinical observations regarding the strength of the respiratory muscular apparatus in cases of asthma or emphysema, not complicated by heart failure, the maximum expiratory pressure is normal, in spite of factors which tend to obstruct expiration.

CONCLUSIONS

1. A new spirometric procedure of investigating the respiratory function, that adds to the factor of volume those of time and pressure, is described.

2. By measuring at the same time as the vital capacity the minimum duration of the quickest possible exhalation of a volume equal to the vital capacity, we obtain the velocity of spirometric respiration by dividing the vital capacity by the expiration time. The velocity of spirometric respiration is that air volume that enters the spirometer per second. It represents the average of the quickest possible expiration. Furthermore, the maximum expiratory pressure is measured; this corresponds to the respiratory movement, and is, in a sense, identical with the vital capacity.

3. The standard values for healthy persons for each of the respiratory factors, as well as the correlations between them, are established. There is no relation between the vital capacity (volume) and the expiratory pressure (strength), i.e., they are independent of each other, whereas the velocity of spirometric respiration depends on the vital capacity, as well as on the expiratory pressure.

4. Any decrease in vital capacity that is caused predominantly by cardiac disease is characterized by prolongation of the expiration time, decrease in the velocity of spirometric expiration, and, above all, by a marked decrease in the expiratory pressure that, in typical cases, sinks below half the standard value.

5. Decreases in vital capacity that are caused primarily by pulmonary disease are characterized by a more marked prolongation of expiration time, by a distinct decrease in the velocity of respiration, and, most of all, by the fact that the expiratory pressure is normal or hardly altered.

6. The decrease in expiratory pressure in cases of cardiac insufficiency is explained by a diminution in the strength of the respiratory muscular apparatus.

7. The diagnostic signs (spirometric data) relating to the specific differences between diminution of vital capacity caused by cardiac and pulmonary diseases are established, and the concept of pseudonormal vital capacity is defined.

8. The fact that a person has a normal vital capacity does not prove that he has a normal respiratory function. Other factors, such as time, velocity, and expiratory pressure, must be considered.

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THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF LANATOSIDE C UPON THE OUTPUT, DIASTOLIC VOLUME, AND MECHANICAL EFFICIENCY OF THE FAILING HUMAN HEART*

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DURING a study of the response of patients with heart failure and normal sinus rhythm to the intravenous administration of lanatoside C,¹ it was noted that the volume of the pulse increased within thirty minutes after injection of the drug. Subsequent observation showed that this alteration in pulse volume was associated with an elevation of pulse pressure, a decrease in the circulation time, and sometimes with a significant drop in the venous pressure within one-half to two hours after administration of the drug. Since an increase in cardiac output might well account for these phenomena, it was decided to check this function and other circulatory measurements before and after the intravenous administration of lanatoside C‡ to patients with severe heart failure and normal sinus rhythm.

When the action of a digitalis glycoside is studied in the laboratory on an experimental animal, a mercury manometer is used to measure the systolic and diastolic blood pressure in the carotid artery; a cardiometer is fitted over the ventricles in order to ascertain the systolic and diastolic heart volumes (the difference between the two is equal to the sum of the output of the left and right ventricles); a stromuhr records the volume of blood flow; and the venous pressure in the right auricle is measured with a water manometer.

In investigating the effect of lanatoside C upon a Starling heart-lung preparation,² we noted that the addition of a little chloroform to the air which is going to the lungs of this preparation causes the heart to dilate and the venous pressure in the left and right auricles to rise. The blood pressure remains constant because of the constant resistance in the system, and the stroke and minute output may remain the same or decrease moderately. (This experiment is the paradigm of acute heart failure of moderate degree.) If lanatoside C is now added to the blood leaving the venous reservoir, the dilatation of the heart soon disappears, the venous pressure falls to normal, and the output of the

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‡Cedilanid, Sandoz Chemical Works, Inc.

heart increases. If large amounts of chloroform are taken up by the blood passing through the lungs, much greater dilatation is produced, the venous pressure rises markedly, and the cardiac output decreases materially. (This represents acute heart failure of high degree.) In such a preparation the addition of lanatoside C to the circulating blood usually causes some decrease in the diastolic volume of the dilated heart and in the venous pressure. If the cardiac output has been markedly reduced, it may or may not increase after the lanatoside has been added; rarely will it return to the previous normal value.

Experimental studies of the effect of digitalis upon the output of the heart depend upon the state of that muscle when the drug is given. Schweigk³ showed that the hypodynamic frog heart responds to the administration of digitalis lanata with an increase in minute volume. Similarly, failing heart-lung preparations of both cats and dogs respond to digitalis with an increase in the cardiac output and a decrease in the heart volume. Bijlsma and Roessingh⁴ and Plant⁵ found that strophanthin diminished the size and increased the stroke output of failing hearts which had been poisoned with chloral hydrate or phosphorus. Similar observations have been reported by Cohn and Steele⁶ and by Anitschow and Trendelenburg.⁷ Peters and Visscher⁸ and Moe and Visscher⁹ have demonstrated that digitalis and lanatoside C increase the mechanical efficiency of a failing heart-lung preparation. In these investigations the work of the heart was kept constant, and it was noted that the administration of the cardiac glycoside produced a decrease in the diastolic volume of the heart and a diminution of its oxygen consumption per gram meter of cardiac work. Such experiments prompted us to study, in man, changes in cardiac output, diastolic heart volume, venous pressure, work of the heart, etc., after the intravenous administration of lanatoside C.

Reports on the action of cardiac glycosides upon the stroke output of the human heart in the presence of failure are contradictory. Some investigators have found that the minute volume was increased, others have reported that it was decreased, and some could detect no change. Stewart and his co-workers,¹⁰ using the Grollman acetylene technique¹¹ for measurement of the cardiac output, found an increase in cardiac output and a decrease in the area of the roentgenographic shadow of the heart. Grassmann and Herzog¹² followed changes in the stroke output of the hearts of decompensated patients who received strophanthin, intravenously, using both the acetylene technique and the method of Broemser and Ranke.¹³ In many instances they noticed an increase in cardiac output within fifteen minutes after injection of the drug.

Harrison and his associates,¹⁴ however, failed to secure consistent results with the Grollman method. McGuire, Hauenstein, and Shore,¹⁵ who employed both the direct Fick¹⁶ and the Grollman technique, also found that the effect of digitalis upon the cardiac output was variable.

In our opinion, the actual stroke output of the left ventricle cannot be measured accurately by the Grollman technique, or even by the direct Fick method if aortic or mitral insufficiency is present. These procedures measure only the amount of blood that moves onward in the aorta. The methods of Broemser and of Bazett, et al.,¹⁷ measure the output of blood from the left ventricle in the presence of aortic insufficiency, but do not account for all the blood pumped by the left ventricle when there is mitral insufficiency. It is possible that some mitral regurgitation may occur in many cases of heart failure associated with dilatation of the left ventricle, and the methods just mentioned will not measure ventricular output accurately in such instances.

Keys and Friedell¹⁸ have perfected an ingenious method of ascertaining cardiac output from roentgenkymographic measurements. Configurations of the heart during systole and diastole are traced from the roentgenkymograms, and the diastolic and systolic areas are then measured with a planimeter. The diastolic and systolic volumes of the heart can be computed from the planimetric measurements by means of the Keys and Friedell formula. The difference between the diastolic and systolic volumes is an index of the cardiac output.

The teleoroentgenkymogram supplies data analagous to those secured from cardiometer tracings of the heart-lung preparation, for both measure changes in systolic and diastolic heart volume. Measurements of venous and arterial pressure in man are comparable to those of right auricular and aortic pressure in the heart-lung preparation. The work done by a heart-lung preparation can be computed for any given period from the product of the stroke output times the mean blood pressure. In man, measurement of the work of the left ventricle in gram meters can be calculated by multiplying the stroke output by the mean blood pressure.

The diastolic volume of normal and pathologic hearts can be ascertained accurately by the roentgenkymographic method of Keys and Friedell, but the true systolic volume cannot be ascertained by this method because the roentgenkymograph records the shortening of cardiac diameters only in the transverse direction, and not in the sagittal. For this reason, the difference between the diastolic volume and this modified systolic volume turns out to be approximately the output of one ventricle, rather than of two. Keys' formula will give accurate values for the cardiac output of one ventricle of the average normal heart, but it cannot be said that this formula will accurately estimate the cardiac output of one ventricle in all types of heart disease. However, the teleoroentgenkymogram does show the increase in cardiac output associated with aortic and mitral regurgitation which the foreign gas methods cannot measure. In our experiments we used the technique described by Keys and Friedell because we hoped to measure the changes in both the diastolic heart volume and cardiac output after the intravenous administration of lanatoside C.

Increases or decreases in the diastolic volume of the heart are important because, as Starling and Visscher¹⁹ and Hemmingway and Fee²⁰ have demonstrated, the oxygen consumption of the heart muscle is directly proportional to its diastolic fiber length. From measurements of the oxygen consumption of the heart and the actual work done by the heart, its mechanical efficiency can be computed. When there is cardiac enlargement, the stroke volume of the left ventricle, as obtained by the Keys and Friedell formula, may not be numerically exact, but changes in the amplitude of cardiac contraction in the transverse direction are obvious at a glance (Figs. 1, 2, 3). Any change in the outline of the cardiac border in the frontal plane must be accompanied by comparable changes in its sagittal dimensions, and hence successive output estimations from kymograms should be reliable indices of the direction (sense) and magnitude of any change in the output of the heart. If

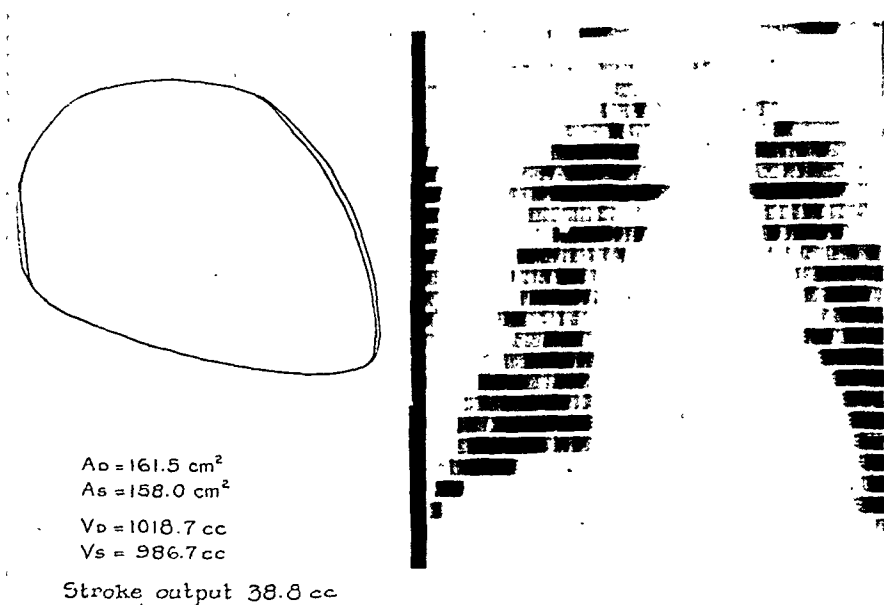


Fig. 1.—Roentgenkymogram of R. A. and derived planimeter tracings of the systolic and diastolic heart areas before the intravenous injection of lanatoside C.

the calculated work of the left ventricle increases while its diastolic volume decreases or remains the same, it is reasonable to assume that the oxygen consumption has not increased, and, therefore, this increase in work represents an improvement in mechanical efficiency.

For our study of cardiac output, ten patients with severe congestive failure (Class 3) and normal sinus rhythm were given two to eight days' preparatory rest in bed, with the fluid intake restricted to 800 c.c. daily. Daily measurements of venous pressure, vital capacity, apical rates, etc., were recorded on individual charts, and the cyanide or decholin circulation time, and blood pressure, were taken frequently. All measurements were again secured shortly before the first teleoroentgen-

kymogram was made. Then 8 c.c.* of lanatoside C were given intravenously, and the measurements were repeated at 5- to 10-minute intervals. A second kymogram was taken thirty minutes to two hours after injection of the drug, depending upon the response of the patient.

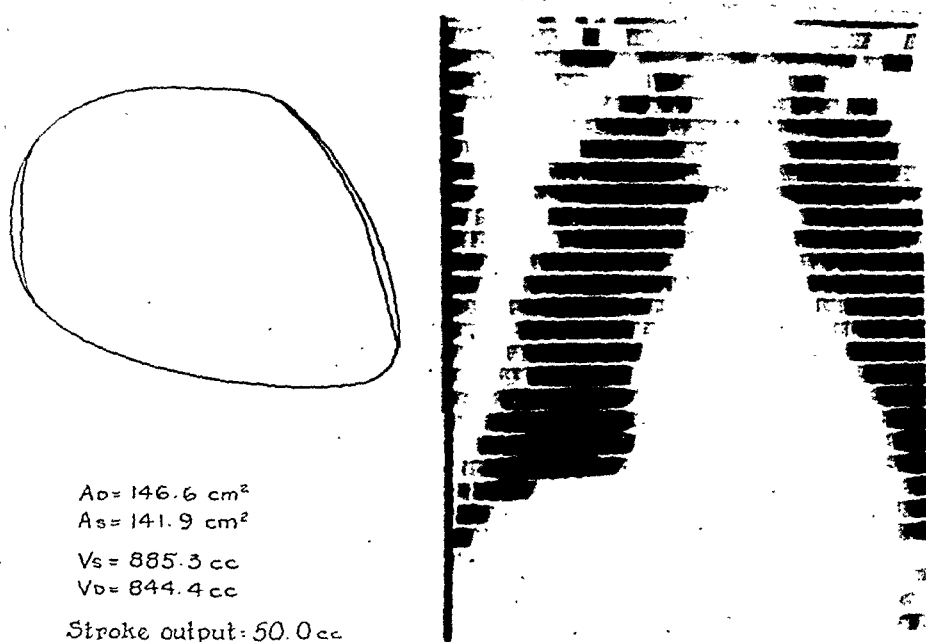


Fig. 2.—Roentgenkymogram of R. A. and derived planimeter tracings of the systolic and diastolic heart areas 2 hours after the intravenous injection of lanatoside C.

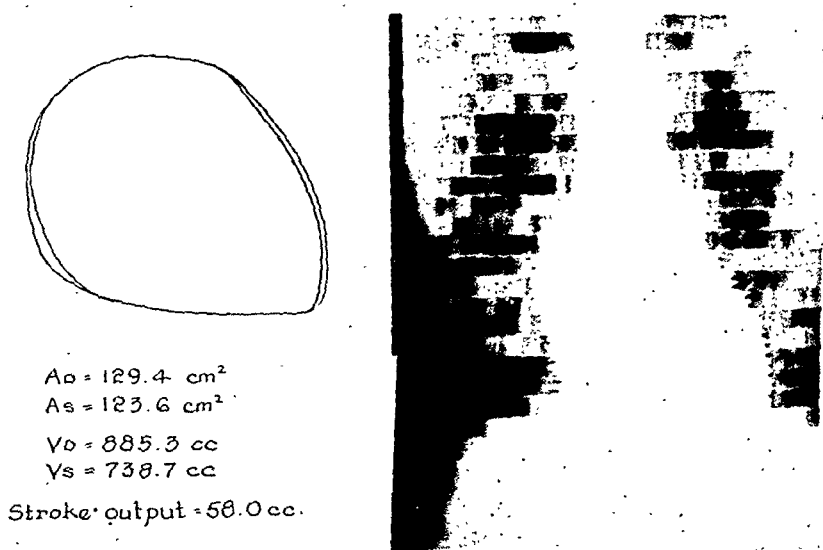


Fig. 3.—Roentgenkymogram of R. A. and derived planimeter tracings of the systolic and diastolic heart areas 19 days after the intravenous injection of lanatoside C.

Table I presents average values of the clinical and kymographic measurements before and after the administration of lanatoside C, and

*Each cubic centimeter of solution contains 0.20 mg. One Hatcher-Brody cat unit is contained in approximately 0.25 mg. of the drug.

TABLE I

AVERAGES OF THE CIRCULATORY MEASUREMENTS MADE ON TEN PATIENTS BEFORE THE INTRAVENOUS INJECTION OF LANATOSIDE C, TWO HOURS AFTER THE INJECTION, AND, IN 7 CASES, AT THE TIME OF DISCHARGE. TWO PATIENTS WERE RESTUDIED 3 AND 13 MONTHS, RESPECTIVELY, AFTER THE INTRAVENOUS INJECTION OF LANATOSIDE C

TIME	PULSE PRESS.	CIRC. TIME	VEN. PRESS.	DIAST. HT. VOL. IN C.C.	STROKE OUTPUT	MIN. VOL.	WORK PER BEAT IN GM. MTRS.	NO. OF CASES
Before Lanatoside C	45.2	34.0	20.3	1021	44.4	4.2	67.6	10
1-2 hr. after Lanatoside C	*73.3	*26.6	*15.0	986	54.6	5.0	*94.7	10
At discharge	*76.2	*30.0	*6.2	*755.5	55.8	4.3	*94.0	7
3-13 months later	73.0	21.05	6.5	691	58.2	4.8	102	2

*Starred numbers represent average values which have been shown by statistical analysis (the "t" test) to be significantly different from average values obtained from measurements taken at the start of the experiment. Values for the two patients restudied three and 13 months later were not analyzed.

shows the trend of reaction in the ten patients. The pulse pressure usually rose, the circulation time and venous pressure decreased, and the stroke and minute output rose slightly. The work of the heart increased while the diastolic volume decreased slightly, indicating a corresponding improvement in mechanical efficiency.

Table II presents individual data for each patient and affords a more accurate appraisal of our results. In eight of the ten patients there was an increase of 30 to 140 per cent in the stroke output of the heart; this was associated with work increments of 30 to 130 per cent, while the size of the heart remained unchanged or decreased. Consequently, these eight patients exhibited a definite improvement in the mechanical efficiency of the heart within 30 to 120 minutes after the injection of 8 c.c. of lanatoside C. In the other two patients the changes were slight, but in both the minute volume of the heart was so large before the administration of lanatoside C that no great increase was to be expected after giving the glycoside.

Roentgenkymographic output studies on seven patients (who received maintenance doses of 1 to 5 tablets* of lanatoside C daily) were repeated three to six weeks after the intravenous injection of the drug. Data obtained at this time are presented in Table III. There was no significant increase in the average stroke output, but the average diastolic heart volume had decreased more than 200 c.c. This represents a further improvement in the mechanical efficiency of the hearts of these patients, for the hearts were doing approximately the same amount of external work with a diminished diastolic volume, and hence with less oxygen consumption. In other words, these hearts were utilizing considerably smaller quantities of energy to perform the same external work.

*The tablets used in this study contained 0.25 mg.

TABLE II

INDIVIDUAL CIRCULATORY MEASUREMENTS BEFORE, AND 1½ TO 2 HOURS AFTER, THE INTRAVENOUS INJECTION OF LANATOSIDE C

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/BEAT
<i>C. H. Coronary Disease</i>										
1:20 p.m.	132/84	48	96	28	21	1068	66.0	6.2	4,608	95
2:12	Injection 8 c.c. lanatoside C									
4:13	134/80	54	92	25	7.5	1007	57.0	5.3	4,968	84
% Increase		12%		-11%		-6%	-14%	-15%	8%	-12%
Inconclusive 2 hours after injection										
<i>C. F. Hypertension and Coronary Disease</i>										
8:40 a.m.	120/96	24	96	46	22	973	24.0	2.3	2,300	35
9:30	Injection 8 c.c. lanatoside C									
10:30	158/100	58	90		12	833	32.2	2.9	5,200	57
% Increase		140%				-14%	34%	26%	126%	62%
Mechanical efficiency increased more than 75%										
<i>J. B. Syphilitic Aortitis, Aortic Insufficiency</i>										
3:00 p.m.	170/96	74	92	42.5	27	1168	30.6	2.8	6,808	54
3:10	Injection 8 c.c. lanatoside C									
4:20	196/76	120	92	24.7	19	1211	70.2	6.5	11,040	131
% Increase		62%		42%		4%	130%	132%	62%	142%
Mechanical efficiency increased 138%										
<i>J. H. Hypertension and Coronary Disease</i>										
3:40 p.m.	134/94	40	102	38.2	24	1016	47.6	4.9	4,080	74
3:45	Injection 8 c.c. lanatoside C									
4:35	160/98	62	100	29.4	20	1044	59.2	6.0	6,200	105
% Increase		55%		23%		3%	24%	22%	52%	42%
Mechanical efficiency increased 39%										
<i>A. C. Syphilitic Aortitis, Aortic Insufficiency</i>										
1:55 p.m.	144/108	36	100	26.2	18	1060	38.2	3.8	3,200	65
2:05	Injection 8 c.c. lanatoside C									
3:30	182/112	70	88	16.2	12	1046	51.2	4.5	6,160	102
% Increase		94%		38%		-2%	34%	18%	92%	54%
Mechanical efficiency increased 59%										
<i>R. A. Syphilitic Aortitis, Aortic Insufficiency</i>										
2:15 p.m.	132/60	72	104	35.9	19	1019	38.8	4.0	7,488	52
2:30	Injection 8 c.c. lanatoside C									
3:00	154/56	98	104	24.5		885	50.0	5.2	10,192	74
% Increase		36%		-32%		-13%	29%	30%	36%	42%
Mechanical efficiency increased more than 55%										
<i>H. S. Hypertension and Coronary Disease</i>										
2:00 p.m.	126/108	18	108	26	14	1042	51.0	5.5	1,944	81
2:15	Injection 8 c.c. lanatoside C									
3:15	144/98	46	107	20.4		1025	49.0	5.2	4,922	80
% Increase		155%		20%		-1.5%	-4%	-6%	153%	-1%
Inconclusive 1 hour after injection										

BL.P.—Blood pressure in mm. Hg

P.P.—Pulse pressure in mm. Hg

H.R.—Heart rate per minute

C.T.—Circulation time in seconds

V.P.—Venous pressure in cm. of water

D.H.V.—Diastolic heart volume in c.c.

S.O.—Stroke output in c.c.

M.O.—Minute output in liters

P.P. × H.R.—Pulse pressure times heart rate

Work/beat—Mean blood pressure times stroke output in gram meters

TABLE II—CONT'D

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
<i>H. J. Coronary Arteriosclerosis</i>										
2:50 p.m.	90/76	14	90		18	1015	48.0	4.3	1,260	54
3:00	Injection 8 c.c. lanatoside C					1044	59.0	5.4	2,392	77
3:15	110/84	26	92							
% Increase		85%				3%	23%	25%	90%	43%
Mechanical efficiency increased 40%										
<i>F. S. Hypertension and Coronary Disease</i>										
2:00 p.m.	108/82	26	104	59.2	21	997	37	3.8	2,704	47
2:10	Injection 8 c.c. lanatoside C					873	46	4.5	5,880	81
2:45	160/100	60	98	33.2	22					
% Increase		140%		44%		-13%	24%	18%	117%	72%
Mechanical efficiency increased more than 85%										
<i>L. P. Hypertensive Heart Disease</i>										
9:40 a.m.	190/90	100	77	25.9	9	849	63	4.8	7,700	119
10:01	Injection 8 c.c. lanatoside C					792	73	4.5	9,642	156
10:36	236/80	156	62							
% Increase		56%				-6.7%	16%	-6%	25%	31%
Mechanical efficiency increased more than 37%										

Further consideration of the data obtained from the patients who were restudied is suggestive. In three instances the minute outputs at the height of congestive failure were greater than they were three to six weeks later, when the patients had apparently recovered, although, as previously noted, an immediate increase in stroke volume had been found two hours after the intravenous injection of lanatoside C.

Two of these same patients were available for kymographic studies three and thirteen months after the first control measurements were obtained. Both were fully compensated at this time. In one patient (C. H.) the stroke output was slightly elevated, but, in the other (F. S.), it had decreased approximately to the value obtained before any cardiac glycoside had been given. The diastolic volume, however, was 300 c.c. less than at the time of the control kymogram in both instances (Tables II and IV).

These facts suggest a possible explanation of the inconstancy of results in cardiac output studies before and after the disappearance of congestive heart failure. It may be that significant changes in cardiac output should be looked for during the period of transition between a state of congestive failure and of compensation. In accordance with the backward failure theory, expounded by Harrison,¹⁴ changes in cardiac output of small degree which occur in a relatively short period of time may result in extensive venous congestion. Similarly, relatively small increments in minute volume during a comparatively short time should result in prompt lessening of the symptoms and signs of pulmonary and venous congestion. The fact that the increases in cardiac output which occurred immediately after the administration of lanatoside C were not always permanent is consistent with this impression.

TABLE III

INDIVIDUAL CIRCULATORY MEASUREMENTS BEFORE, AND 3 TO 6 WEEKS AFTER, THE
INTRAVENOUS INJECTION OF LANATOSIDE C, WHEN THE PATIENTS HAD
BECOME COMPENSATED

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
12/21/40	<i>L. P., Female, Age 68, Hypertensive Heart Disease</i>									
Control	190/90	100	77	25.9	9	849	63	4.8	7,700	119
1/11/41	210/92	118	62	25.8	6	838	106	6.6	7,316	226
% Increase		11.8%				-1%	68%	39%	-5%	90%
11/29/40	<i>C. F., Male, Age 61, Hypertensive and Arteriosclerotic Heart Disease</i>									
Control	120/96	24	96	46	22	973	24	2.3	2,300	35
12/21/40	120/84	36	76	27.3	6	728	41	3.1	2,636	57
% Increase		50%				-25%	73%	35%	15%	63%
2/8/40	<i>J. H., Male, Age 63, Hypertensive and Arteriosclerotic Heart Disease</i>									
Control	134/94	40	102	38.2	24	1016	47.6	4.9	4,080	74
3/4/40	152/80	72	88	17.5	6	739	39.2	3.5	6,336	63
% Increase		80%		-54%		-27%	-19%	-28%	55%	-17%
1/30/40	<i>H. J., Male, Age 69, Arteriosclerotic Heart Disease</i>									
Control	90/76	14	90	74.3	18	1016	47.6	4.3	1,260	54
3/4/40	90/88	12	88	79.6	10	740	39.2	3.5	1,056	48
% Increase		-14%		6%		-27%	-17%	-18%	-16%	-10%
2/15/40	<i>A. C., Male, Age 51, Syphilitic Heart Disease, Aortic Insufficiency</i>									
Control	140/108	32	100	26.2	18	1060	38.2	3.8	3,200	65
3/4/40	158/100	58	78	15.8	8	723	31.7	2.5	4,524	56
% Increase		81%		-40%		-31%	-17%	-34%	41%	-15%
2/13/40	<i>R. A., Male, Age 46, Syphilitic Heart Disease, Aortic Insufficiency</i>									
Control	132/60	72	104	35.9	19	1019	38.8	4.0	7,488	50
3/4/40	170/60	110	76	24.5	3.6	738.7	58	4.4	6,840	90
% Increase		48%		-32%		-37%	49%	10%	-8%	80%
1/30/40	<i>F. S., Male, Age 69, Hypertensive and Arteriosclerotic Heart Disease</i>									
Control	108/82	26	104	59.2	21	997	37	3.8	2,704	47
3/4/40	160/76	84	76	27.5	5.6	782	75.5	5.74	6,384	121
% Increase		215%		-53%		-21%	140%	50%	136%	150%

TABLE IV

INDIVIDUAL CIRCULATORY MEASUREMENTS FROM 2 PATIENTS BEFORE THE INJECTION
OF LANATOSIDE C AND AFTER 3 AND 13 MONTHS

TIME	BL.P.	P.P.	H.R.	C.T.	V.P.	D.H.V.	S.O.	M.O.	P.P. × H.R.	WORK/ BEAT
1/30/40	<i>F. S., Male, Age 69, Hypertensive and Arteriosclerotic Heart Disease</i>									
Control	108/82	26	104	59.2	21	997	37	3.8	2,704	47
3/1/41	180/110	70	66	23.6	7.0	686	37.3	2.5	4,620	75
% Increase		169%		-58%		-31%	1%	-35%	71%	60%
12/30/40	<i>C. H., Male, Age 69, Arteriosclerotic Heart Disease</i>									
Control	132/84	48	96	28	21	1068	66	6.2	4,608	95
3/1/41	158/82	76	90	18.5	6.0	695	79	7.1	6,840	129
% Increase		58%		-34%		-35%	16%	14%	45%	36%

BL.P.—Blood pressure

P.P.—Pulse pressure

H.R.—Heart rate

C.T.—Circulation time

V.P.—Venous pressure

D.H.V.—Diastolic heart volume

S.O.—Stroke output

M.O.—Minute output

P.P. × H.R.—Pulse pressure times heart rate

Work/beat—Mean blood pressure times stroke output in gram meters

The much smaller diastolic heart volume in our patients after the establishment of compensation is significant, and is in accord with the results of Stewart and his co-workers.¹⁰

CONCLUSIONS

1. The intravenous administration of lanatoside C to patients with heart failure and normal sinus rhythm usually increases the pulse pressure and reduces the circulation time and venous pressure within two hours. Roentgenkymographic studies of the hearts of ten such patients showed that the drug produced a significant reduction of diastolic heart volume in five patients and an increase in stroke output in eight patients. In two patients, the minute volume of the heart was so large before the administration of the drug that no great increase could be expected.

2. In the eight patients who responded with increased cardiac output, the product of the stroke output and the mean blood pressure was definitely increased, whereas the diastolic heart volume decreased or was unchanged. Since the diastolic heart volume is an index of oxygen consumption, these increases in work which resulted from the administration of lanatoside C must have represented proportional improvement in the mechanical efficiency of the hearts of eight of the ten patients studied.

3. In seven patients who were restudied after the establishment of compensation, there was a decrease of 200 c.c. or more in the diastolic heart volume. In four patients, the minute volume was greater than at the start of the experiment, and in three patients it was less.

4. The most consistent and lasting change in the failing heart that is produced by the administration of lanatoside C seems to be a decrease in its diastolic volume, or oxygen consumption.

We wish to thank Dr. Ancel Keys and his staff for their invaluable assistance in making the planimetric measurements from the teleoroentgenkymograms, in applying the Keys and Friedell formula to the obtained data, and for their generous help in carrying out some of the experiments.

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THROMBOSIS OF THE SUBCLAVIAN AND AXILLARY VEINS

REPORT OF 46 CASES

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THROMBOSIS of the veins of the lower extremity is so frequent as to be a matter of common experience. The same condition in the veins of the upper extremity seems to be so relatively infrequent that a single investigator's experience is limited to a few cases. However, thrombosis of the subclavian and axillary veins is perhaps more common than is generally realized. In point of fact, one of us (J. R. V.) has previously reported¹ 17 such cases, and in the past three years we have observed 29 additional cases. It is our purpose in this report to present the data obtained from the study of all 46 cases.

The clinical manifestations of thrombosis of the subclavian and axillary veins vary, depending on whether the obstruction develops acutely or gradually. In the cases in which the thrombosis begins acutely, pain is usually the initial symptom. The pain begins in the region of the shoulder and extends down the arm to the hand. This generalized pain and the cyanosis and coldness of the finger tips which appear almost simultaneously are the result of vasospasm. Weakness and numbness of the extremity develop, and the weakness may progress until the function of the arm is lost. Within a short time, swelling of the hand and arm becomes apparent and may increase rapidly, so that the affected extremity sometimes reaches twice its normal size within a few hours. The pulse rate is usually normal unless there is some other cause for tachycardia. The systolic blood pressure is often 10 to 15 mm. higher on the affected side than in the normal arm. There are local pain and tenderness over the thrombosed portions of the involved veins. Because of the edema, the superficial veins of the arm are not readily seen, but the antecubital veins usually are palpably distended. The initial pressure in these veins is invariably above normal (usually more than 300 mm. of saline), and rises promptly to a higher level when the patient opens and clenches the fist repeatedly while the venous pressure is being measured.² The circulation time from the involved extremity to the lung or tongue is prolonged. The oxygen content of the venous blood is decreased. A venogram will reveal the obstruction, the extent of involvement of the veins, and the developing collateral venous channels.

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After acute thrombosis of the subclavian and axillary veins, the generalized pain in the arm and cyanosis of the digits disappear as soon as vasospasm is released. This usually takes place promptly after beginning appropriate treatment. The relief of edema and weakness depends upon re-establishment of the circulation, and is necessarily a slower process. The rapidity of improvement at this stage varies primarily with the location and extent of the thrombosis, and secondarily, with the number and size of collateral channels.³ In cases in which only a short segment of the subclavian or axillary vein is involved, collateral venous channels soon begin to function, the venous pressure falls, and the edema disappears within five to seven days. In cases of more extensive involvement, the venous pressure remains elevated because of inadequacy of the collaterals, so that the edema subsides more slowly and tends to recur with exercise. In some cases the edema never disappears completely. In such cases, and in those in which there is an abnormal elevation of local venous pressure with exercise, use of the arm soon results in fatigue or even pain. The postthrombotic stage after acute thrombosis of the subclavian and axillary veins then resembles closely the clinical picture which develops in cases of gradual occlusion of these veins.

Gradual occlusion of the subclavian and axillary veins is almost always secondary to some other disease, usually a malignant neoplasm involving the thorax. In some cases, therefore, the manifestations of the venous obstruction may be overshadowed by the primary disease. The first symptoms of thrombosis which develops gradually are usually slight enlargement and fatigability of the affected arm. The swelling of the arm may be comparatively slight, and pitting edema is not necessarily present. Vigorous or prolonged use of the arm may cause an increase in the swelling or may be impossible because of the fatigue which results from exercise. Collateral veins appear over the upper part of the arm, the shoulder, and the chest, and the veins of the forearm and hand are obviously engorged with blood. The initial venous pressure in the affected arm is higher than normal, but usually below 300 mm. of saline. Exercise of the hand produces a further elevation of the venous pressure.² The circulation time from the affected arm to the lung or tongue may be prolonged, but is often within normal limits. As in cases of acute thrombosis, the venogram will reveal the obstruction and the extent of involvement of the veins, and the collateral venous channels will be visualized. In the cases in which gradual occlusion is secondary to a malignant neoplasm, the progress of symptoms in the affected arm is variable. As the neoplasm grows, the thrombosis may spread, with a consequent aggravation of symptoms. In some cases the clinical picture will suddenly change from one of gradual occlusion to one of acute obstruction.

An etiologic classification of cases of thrombosis of the subclavian and axillary veins offers some difficulty. We have listed our cases in

groups which represent the major causative factors (Table I). It must be understood that in some instances more than one factor is important in the pathogenesis of the disease.

TABLE I
CLASSIFICATION OF 46 CASES OF SUBCLAVIAN AND AXILLARY VEIN THROMBOSIS

	CASES
A. Thrombosis complicating heart failure	16
1. Stasis thrombosis	13 cases
2. Chemical thrombosis	2 cases
3. Thrombosis secondary to local infection	1 case
B. Traumatic, or effort, thrombosis	10
C. Thrombosis secondary to neoplasm	18
D. Thrombosis from operative scar	2
	46

THROMBOSIS COMPLICATING HEART FAILURE

Thrombosis of the peripheral veins is a common complication of congestive heart failure. The presence of such thrombosis is often unrecognized because of the prominence of the manifestations of heart failure. Its importance has not been generally emphasized. However, Hampton and Castleman⁴ showed that of 370 autopsy cases of pulmonary embolism 30 per cent were cardiac patients. The source of a very large percentage of the emboli in these cases was "symptomless" thrombosis of the deep veins of the legs. This study and White's⁵ experience indicate the extreme importance in heart failure of peripheral venous thrombosis as a cause of death from pulmonary embolism, or as a cause of prolongation of the period of heart failure in cases in which pulmonary embolism is not fatal.

Thrombosis of the veins of the upper extremity is quite infrequent as compared with the lower extremity. In a statistical study⁶ of 1,260 cases of postoperative venous thrombosis involving 1,401 locations, Barker, et al., found that the veins of the lower extremity were the site of 85.6 per cent of the thromboses, whereas involvement of the veins of the upper extremity constituted only 1.7 per cent of the total. Thrombosis of the veins of the upper extremity in cases of heart failure has rarely been mentioned in the literature. Since 1900, when Welch reviewed the subject⁷ and reported several cases that he had personally observed, there has been no important consideration of the condition. However, our experience has led us to believe that it is a more frequent complication than is indicated by the sparsity of reports. In the past five years we have observed 16 cases of subclavian and axillary vein thrombosis complicating heart failure (Table II).

In all of these 16 cases the slowing of the venous circulation that accompanies heart failure was undoubtedly important in predisposing to venous thrombosis, and in 13 of the cases it was the only apparent causative factor. In 2 of the cases "chemical" thrombosis, caused by

TABLE
SUBCLAVIAN AND AXILLARY VEIN THROMBOSIS

CASE	AGE	SEX	RACE	CARDIAC DIAGNOSIS	DURATION OF HEART FAILURE	LOCATION OF THROMBOSIS	ONSET	SYMPTOMS
1	68	M.	B.	Hypertensive heart disease	3 weeks	Left subclavian	Acute	Edema of left arm
2	71	F.	B.	Hypertensive heart disease	1 year	Left subclavian	Acute	Edema, weakness of left arm
3	48	F.	B.	Syphilitic heart disease	7 months	Left subclavian	Acute	Edema, weakness of left arm
4	40	M.	B.	Hypertensive heart disease; dissecting aneurysm	3 months	Left subclavian	Acute	Edema of left arm
5	67	F.	B.	Hypertensive heart disease (cerebral hemorrhage)	Several days?	Left subclavian and axillary veins	Acute	Edema of left arm
6	65	F.	W.	Hypertensive heart disease	7 months	Left subclavian	Acute	Pain in left shoulder and arm; edema
7	29	F.	W.	Rheumatic heart disease	14 months	Right subclavian	Acute	Pain in right arm; edema
8	30	M.	B.	Syphilitic heart disease	1 year	Right basilic, axillary and subclavian	Acute	Pain in right arm after injection of mercurpurin; ten- derness; edema
9	48	M.	B.	Hypertensive heart disease	2 weeks	Left subclavian and axillary	Acute	Pain in left axilla; edema and weak- ness of arm
10	33	F.	B.	Hypertensive heart disease	2 months	Left subclavian and axillary	Acute	Pain in left pectoral region and arm; edema of left arm and breast; later prominent collateral veins
11	57	M.	W.	Coronary ar- tery sclerosis	3 weeks	Right basilic, axillary and subclavian	Grad- ual	Thrombosis followed numerous injections of mercurpurin; prominent veins at shoulder; hard thrombosed veins

II

COMPLICATING HEART FAILURE

CIRCULATION TESTS		VENO-GRAM	COURSE AND TERMINATION	AUTOPSY
AFFECTED ARM	UNAFFECTED ARM			
V.P. 350 mm.	V.P. 275 mm.		Pulmonary infarction; death	
			Pulmonary infarction? improvement; left hospital	
V.P. 265 mm. C.T. 47 sec.	V.P. 190 mm. C.T. 53 sec.		Pulmonary infarction; improvement; left hospital	
			Pulmonary infarction; dissecting aneurysm; death	Thrombosis of left subclavian vein extending into innominate vein; pulmonary infarction; hypertensive heart disease; dissecting aneurysm
V.P. 335 mm. C.T. 16 sec.	V.P. 110 mm. C.T. 13 sec.		Pulmonary infarction; bronchopneumonia; death	Thrombosis of left subclavian and axillary veins; pulmonary infarction (small); bronchopneumonia; hypertensive heart disease
V.P. 265 mm. V.P.Ex. 360 mm. C.T. 52 sec.	V.P. 235 mm. V.P.Ex. 250 mm. C.T. 40 sec.	Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Intractable heart failure; death	Thrombosis of right subclavian vein extending into internal jugular and innominate veins; multiple pulmonary infarcts; rheumatic heart disease
V.P. 365 mm. V.P.Ex. 390 mm.	V.P. 265 mm. V.P.Ex. 260 mm.	Confirmatory	Death from pulmonary embolism	
V.P. 295 mm. V.P.Ex. 350 mm. C.T. 47 sec.	V.P. 290 mm. V.P.Ex. 290 mm. C.T. 36 sec.		Pulmonary infarction; death	Thrombosis of left subclavian and axillary veins; small pulmonary infarcts; hypertensive heart disease
V.P. 240 mm. V.P.Ex. 390 mm. C.T. Blank	V.P. 115 mm. V.P.Ex. 150 mm. C.T. 11 sec.	Confirmatory	Long course; repeated pulmonary infarction; later thrombosis of left femoral and iliac veins; death	Hypertensive heart disease; cardiac mural thrombi; old thrombosis left innominate, internal jugular, subclavian and axillary vv.; recent thrombosis left iliac and femoral vv.; multiple pulmonary infarcts
		Confirmatory	Improvement; left hospital	

TABLE

CASE	AGE	SEX	RACE	CARDIAC DIAGNOSIS	DURATION OF HEART FAILURE	LOCATION OF THROMBOSIS	ONSET	SYMPTOMS
12	26	F.	B.	Rheumatic heart disease	3 months	Left subclavian, axillary, brachial, and external jugular	Acute	Thrombophlebitis following furuncle over external jugular vein; pain, edema of left arm
13	66	F.	W.	Hypertensive heart disease		Left subclavian and axillary	Acute	Pain, weakness, edema of left shoulder and arm; later collateral veins
14	55	F.	B.	Hypertensive heart disease	Several months	Left subclavian and axillary	Acute	Pain in neck and arm; edema; later prominent collateral veins
15		F.	B.	Hypertensive heart disease	Several days	Left subclavian and axillary	Acute	Pain, edema, coldness of left arm
16		F.	W.	Hypertensive heart disease	Several weeks	Right subclavian and axillary	Acute	Pain, edema, coldness of right arm

V.P. = Venous pressure.

V.P.Ex. = Venous pressure after exercise of hand for one minute.

C.T. = Arm-to-tongue circulation time.

intravenous injections of a mercurial diuretic, extended to the axillary and subclavian veins from the veins of the arm. In one case the thrombosis apparently resulted from spread of infection from a furuncle which lay over the external jugular vein. The cause of the heart disease is apparently not important in the incidence of subclavian and axillary vein thrombosis. Most of our cases were in patients with hypertensive heart disease, but this is to be explained by the greater frequency of this type in the hospitals in which our studies were made. On the other hand, the severity of the heart failure seems to be important in the causation of the venous thrombosis. In all but 2 of the 16 cases, the heart failure was so severe that the patients were bedridden. It is interesting that in 12 cases the veins of the left arm were involved, and in 4 cases, the veins of the right arm. One apparent reason for this disparity of incidence is the longer, more devious course taken by the left innominate vein. Another possible reason is that the patient who is bedridden makes greater use of the right arm than of the left. This incidence is in contrast to that in cases of traumatic thrombosis, in which the veins of the right arm are usually affected.¹

In 15 of the 16 cases the onset of symptoms was acute. In the one case in which the onset was gradual, thrombosis developed after repeated injections of a mercurial diuretic, and there were no outstanding symptoms except prominent collateral veins and hardness of the basilic and axillary veins. In most of the cases in which there was an acute onset, the first symptom was pain in the arm or region of the shoulder. All of the patients rapidly developed edema, usually of severe degree. The significance of edema of one arm in a case of severe heart failure probably is not always immediately appreciated because

II—CONT'D

CIRCULATION TESTS		VENO-GRAM	COURSE AND TERMINATION	AUTOPSY
AFFECTED ARM	UNAFFECTED ARM			
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Gradual improvement; left hospital	
		Confirmatory	Death from heart failure	

of the prominence of the symptoms of heart disease. For this reason, thrombosis of the subclavian and axillary veins may be overlooked. Four patients complained of weakness of the affected arm. It is to be remembered that all of the patients were severely prostrated, so that weakness of one arm was probably not readily noticed. In all cases in which the venous pressure was measured, it was found to be abnormally high on the affected side, ranging from 240 to 365 mm. of saline. In the unaffected arm also the venous pressure frequently was elevated because of heart failure, but usually not to the same extent as on the side of the thrombosis. In all cases in which the "exercise test" was used, there was a prompt and substantial increment in the venous pressure on the affected side, but on the nonobstructed side there was little or no change. For this reason, the "exercise test" has proved to be of particular value in the diagnosis of peripheral venous obstruction complicating congestive heart failure. The circulation time measurements were of little value in confirming the presence of the venous thrombosis.

The course of subclavian and axillary vein thrombosis in cases of heart failure may tend slowly toward recovery, but is commonly interrupted by grave complications. Propagation of the thrombus is favored by the generalized slowing of the venous circulation and by the patient's inactivity. Under these circumstances it is not surprising that embolism is a frequent occurrence. In 9 of the 16 cases in this series, pulmonary embolism occurred, and in 7 it was fatal. In 4 of the 5 autopsy cases the only source that was disclosed for the pulmonary embolism was the thrombus in the subclavian and axillary veins. In the other case there were other sites of thrombosis, any of which may have been the origin of the pulmonary embolism. In the two cases in which the patients died but were not autopsied, the only apparent

source for the pulmonary emboli was in the thrombosed veins of the arm. In the two cases of pulmonary embolism that did not end fatally, there seemed to be considerable aggravation and prolongation of the heart failure as a result of the embolism.

TRAUMATIC, OR EFFORT, THROMBOSIS

The exact pathogenesis of this type of thrombosis remains obscure. In a previous communication one of us reviewed the various theories,¹ and since that time nothing of importance has been added to the knowledge of the subject. Thrombosis may result from a variety of incidents, some trivial, some severe. In some cases there is no obvious preceding effort or trauma. In 8 of the 10 cases which we have classified as traumatic, or effort, thrombosis of the subclavian and axillary veins, the exciting causes include direct contusion of the shoulder region (3 cases), carrying a heavy weight by hand, a fall on the outstretched hand (Fig. 1), working with the arms overhead, washing clothes by hand, and sleeping with the arm outstretched under the head. In the remaining 2 cases there was no definite history of any unusual effort or of direct trauma.

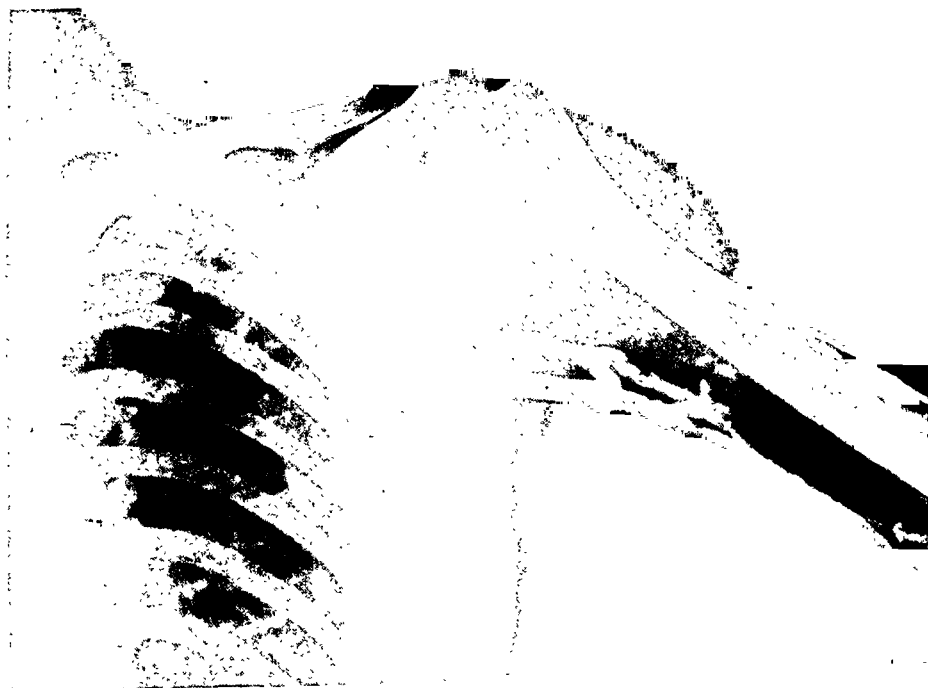


Fig. 1.—Venogram demonstrating acute occlusion of subclavian vein caused by fall on outstretched hand.

Traumatic thrombosis of the veins of the upper extremity is not of frequent occurrence. This can best be judged by the fact that the majority of reports on the subject deal with one or a few cases. The onset of symptoms of this type of thrombosis is acute, and the manifestations and course closely follow the description of acute thrombosis,

as given above. The thrombosis which follows effort almost always occurs on the right side in right-handed persons, and that which follows trauma occurs, of course, on the side that is injured.

Embolism practically never results from this type of thrombosis. This is in direct contrast to the experience with thrombosis which complicates heart failure, and is probably to be explained by the fact that in traumatic, or effort, thrombosis there is no general venous stasis, and the patient usually is not bedridden and uses his arm more actively, so that treatment is effective in limiting propagation of the thrombus.

It should be emphasized that, although collateral circulation usually develops sufficiently to relieve the acute symptoms, there is almost invariably some residual impairment of the circulation. This can be demonstrated objectively by measuring the venous pressure on the affected side during exercise of the hand. In such cases the patient finds that his arm tires quickly or may even become painful during exercise. In some cases edema may reappear after prolonged exertion. Fig. 2 is an example of persistence of postthrombotic manifestations.

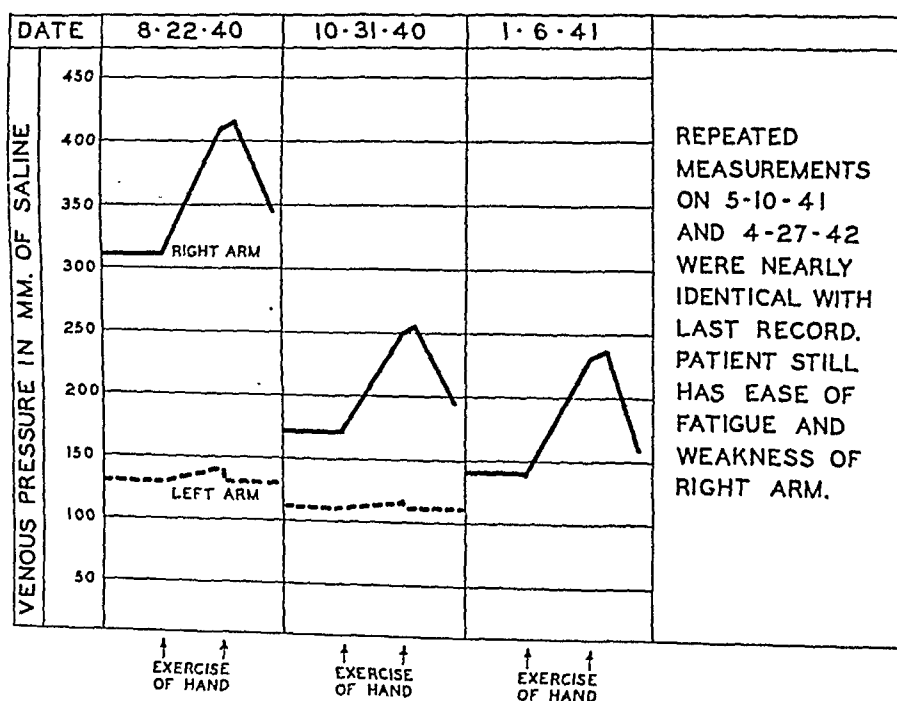


Fig. 2.—Right subclavian and axillary vein thrombosis (traumatic). Onset 8/19/40.

THROMBOSIS SECONDARY TO NEOPLASM

The most common cause of thrombosis of the subclavian and axillary veins is a malignant neoplasm of the chest or axilla. Eighteen of the 46 cases in our series fell in this group. The most common neoplasm was carcinoma of the breast, of which there were 9 cases. This number

is probably smaller than would be expected during five years of experience at a large general hospital, but we have included only cases which we have personally observed. Nor have we included in this report a consideration of the type of axillary vein obstruction which frequently follows the alteration of the course of the axillary veins produced by radical mastectomy. The other types of neoplasm were as follows: bronchiogenic carcinoma, 6 cases; lymphosarcoma, 1 case; sarcoma of the prostate, 1 case; and sarcoma of the ovary, 1 case.



Fig. 34.—Venogram showing occlusion of subclavian, axillary, and basilic veins secondary to metastasis from sarcoma of the prostate. Note numerous small collateral vessels.

It has long been recognized that malignant neoplasms exert an unexplained influence on the coagulation of the blood, so that there is an increased tendency to peripheral venous thrombosis. This may develop without apparent reason at a point distant from the site of the neoplasm. However, we have not observed an instance of subclavian and axillary venous thrombosis secondary to neoplasm in which there was

not an adequate mechanical and anatomic explanation for the involvement of the vein. There may be a direct invasion of the vein by the neoplasm, with obstruction primarily as the result of a filling of the lumen of the vein by the malignant growth. In other cases only the wall of the vein is invaded, and thrombosis follows. In still other cases the malignant lesion is contiguous to the vein, but does not invade it. In this last type of case, thrombosis results from compression or distortion of the vein.

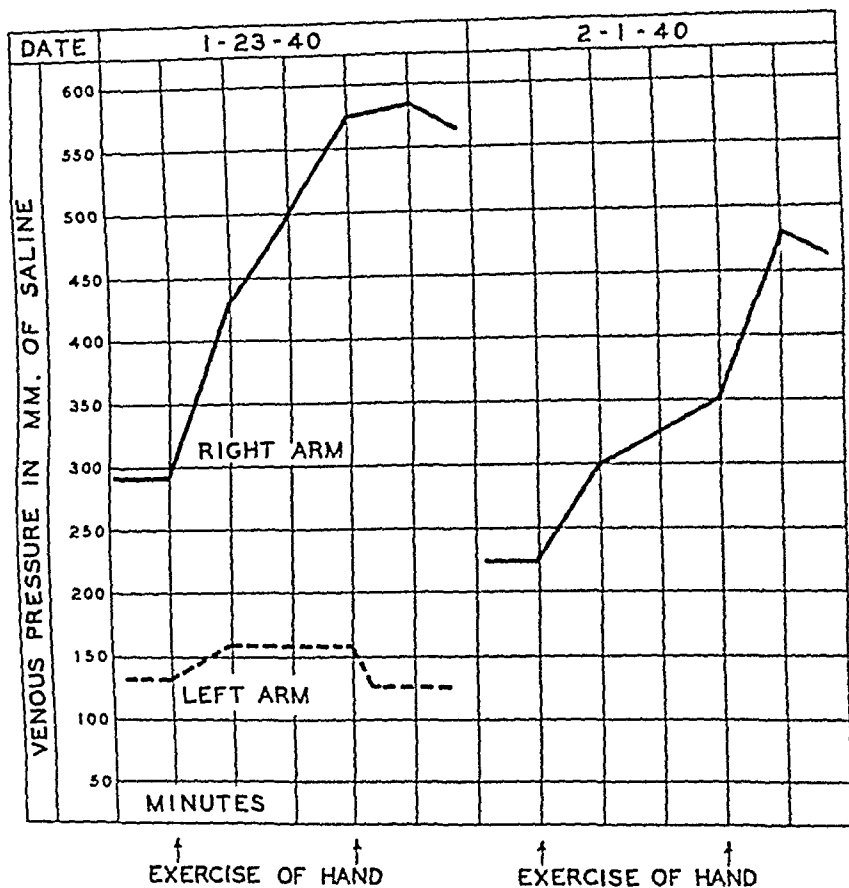


Fig. 3B.—Same case as Fig. 3A, showing difference in venous pressure measurements in the arms. Note the persistent elevation of venous pressure in the affected arm. Right subclavian and axillary vein thrombosis (neoplastic).

In most of the cases of this type of thrombosis, the first symptom noticed by the patient is swelling of the arm, so that the onset seems to be acute. However, in cases in which there has been an opportunity to observe the patient prior to the time of development of acute symptoms, there are often evidences of gradual occlusion of the subclavian and axillary veins. In some there are quite obvious collateral veins at the shoulder region long before the patient is aware of any trouble with the arm. Therefore, although the patient may not seek medical aid until there are acute symptoms, it is probable that in many cases the venous obstruction has been a slowly developing process (Fig. 3A

and B). Of the common types of subclavian and axillary vein thrombosis, that which is secondary to neoplasm is the only one in which the onset of symptoms is usually gradual.

The symptoms of thrombosis secondary to neoplasm differ somewhat from the classical descriptions of acute thrombosis. In the first place, the pain which results from vasospasm in the other types of thrombosis may be entirely absent. However, there is often another type of pain in the shoulder, neck, and arm. This pain is caused by involvement of the brachial plexus by the malignant neoplasm. It is persistent, peculiarly severe, and progressive. Paralysis of the arm may eventually follow such involvement of the brachial plexus. In the second place, the edema which characterizes complete obstruction of the veins shows less tendency to recede, and, indeed, usually becomes progressively more severe. These patients are then subject to recurrent attacks of lymphangitis, lymphadenitis, and cellulitis, such as those which accompany the postthrombotic syndrome in the lower extremity. In the third place, as mentioned in the discussion of the onset, there may be obvious collateral veins before the edema appears. If the patient is not seen until edema has developed, the presence of prominent collateral veins is strong presumptive evidence that a neoplasm has caused the thrombosis.

The course of this type of thrombosis is governed by the progress of the underlying disease, which eventually terminates fatally. As far as we have been able to observe, pulmonary embolism has not resulted from this type of thrombosis. However, pulmonary involvement by the neoplasm, which was present frequently in these cases, may possibly have prevented the recognition of symptoms of pulmonary embolism.

THROMBOSIS FROM POSTOPERATIVE SCARRING

Occasionally, after radical removal of the breast,⁸ thrombosis of the axillary and subclavian veins results from gradual obstruction of the axillary vein by scar tissue. The axillary vein may be obstructed by simple constriction by scar tissue, without actual thrombosis. In other cases, the vein is occluded when the patient's arm hangs down beside the chest wall. This is the result of the alteration in the course of the vein which follows removal of the pectoral muscles. Cases of obstruction of the axillary vein without thrombosis have not been considered in this report. However, in this series of 46 cases, there were 2 in which thrombosis of the axillary vein followed constriction by scar tissue. These cases are described briefly.

CASE REPORTS

M. J., a 66-year-old Negress, was first seen by us in 1939. Three years prior to that time a radical mastectomy had been performed for carcinoma of the left breast. About 10 weeks after the operation, following deep roentgen therapy to the axilla and chest, the patient developed pain along the inner aspect of the left

arm and in the axilla. The entire left upper extremity became swollen. This swelling remained, although it tended to subside somewhat after a period of rest. On examination, the affected arm was obviously enlarged, and there was pitting edema. The veins in the antecubital fossa were large and distended. Other veins in the forearm and hand were obscured by edema. The initial venous pressure in the left antecubital vein was 160 mm. of saline. The pressure rose rapidly and astonishingly, with exercise of the hand, reaching 820 mm. after three minutes (Fig. 4). A venogram showed complete obstruction of the left axillary vein. The patient was seen frequently in the Surgical Outpatient Clinic during the next five months. The swelling of the arm persisted. A repetition of the venous pressure measurement at the end of that time gave an initial reading of 130 mm. After exercise of the hand for one minute, the pressure had risen to 960 mm. Early in 1940 the left axilla was explored, and the axillary vein was found to be incarcerated in dense scar tissue. It was completely occluded by an organized thrombus. The scar tissue was excised as completely as possible, and care was taken not to injure any of the collateral veins. After this operation the swelling of the arm became less severe. When the patient was last seen, in 1942, there was only slight swelling of the left arm. However, after prolonged exercise, the edema recurs.

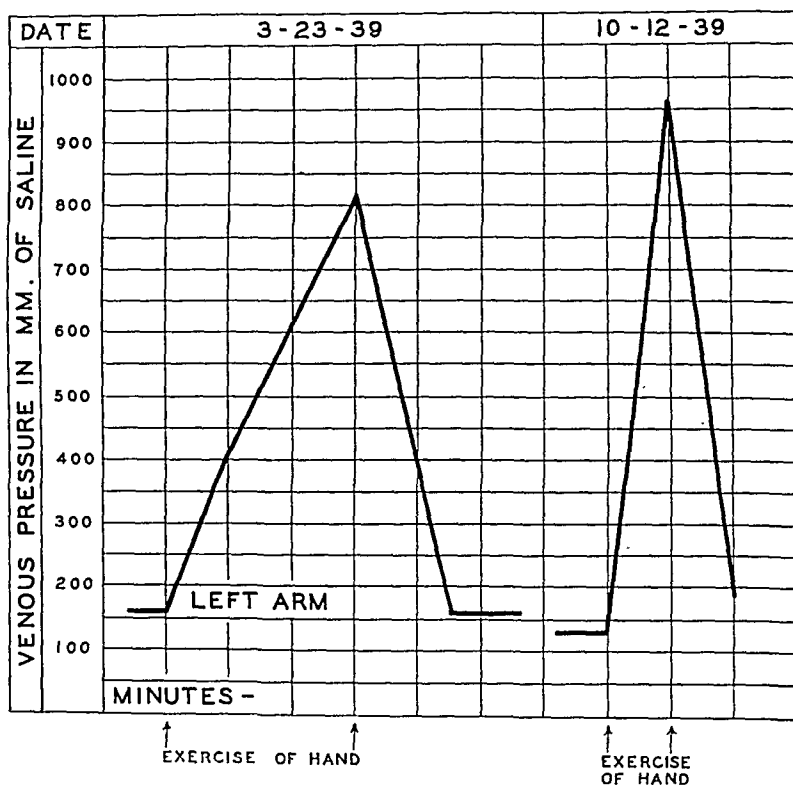


Fig. 4.—Thrombosis of left axillary vein due to constriction by scar of radical mastectomy.

In this case the initial reading of the venous pressure was within normal limits. It was not until the "exercise test" was performed that evidence was obtained that severe venous obstruction was the cause of the edema. Usually, in cases of chronic obstruction of large veins resulting from compression by scar tissue, attempts to relieve the obstruction by means of operation are unsuccessful. However, in this case, there was definite improvement after excision of the scar. Since the axillary vein was occluded by an organized thrombus, the improvement must be attributed to the development of a more adequate collateral circulation.

H. McL., a 68-year-old white woman, was treated in 1932 for carcinoma of the right breast by radical mastectomy and deep roentgen therapy. At an indefinite time after this, the patient noted that the right arm was persistently swollen to a slight degree. By that time, a firmly contracted scar had formed in the right axilla. On several occasions from 1937 to 1942, the right arm became more than usually swollen for a few days at a time, but the patient was not able to ascribe this to any particular activity. In April, 1942, after strenuous use of the right arm and a minor injury to the right elbow, the arm suddenly became painful, tender, and severely swollen. Blotchy areas of redness appeared on the skin, and there was moderate fever. The picture was that of acute lymphangitis and cellulitis superimposed upon chronic venous obstruction. In accordance with our experience in cases of a similar type, in the post-thrombotic syndrome involving the lower extremity,³ the condition was treated by rest in bed, with the arm abducted and elevated on pillows, the application of warm, moist compresses to the arm, and the administration of sulfadiazine. With this treatment, the patient's fever promptly subsided, and, within a few days, the arm resumed its usual appearance. At that time the initial venous pressure was 170 mm. in the right antecubital vein, and 130 mm. in the left. With exercise of the hand for 1 minute, the venous pressure rose to 190 mm. in the right arm, but remained at 130 mm. in the left.

This case is of interest mainly because it demonstrates that the post-thrombotic syndrome involving the upper extremity may be complicated by lymphangitis and cellulitis similar to that which occurs so commonly in cases of chronic obstruction of the deep veins of the lower extremity. The diagnosis of axillary vein thrombosis in this case has not been confirmed by exploration of the axilla, nor has a venogram been made.

SUGGESTIONS ON TREATMENT

During the acute phase of thrombosis of the subclavian and axillary veins, the arm should be elevated, and warm, moist compresses applied. Active movement of the hand should be encouraged. The position of the arm should be changed from time to time in order to prevent fatigue and joint pain. As suggested by Ochsner and DeBakey,⁹ temporary cervicodorsal sympathetic block is helpful in those cases in which there is evident vasospasm. As the symptoms subside, the compresses are discontinued and more active use of the arm is permitted.

Because of the frequency of pulmonary embolism in cases of subclavian and axillary vein thrombosis complicating heart failure, it is suggested that the subclavian vein be ligated proximal to the thrombus. Such an operation is feasible because the subclavian vein can be readily exposed at the base of the neck, under local anesthesia.

When the acute phase has subsided, little or no treatment is necessary. In cases in which there is considerable residual obstruction, the patient may find it necessary to limit the use of his arm in order to avoid fatigue, pain, or recurrence of edema.

SUMMARY AND CONCLUSIONS

Thrombosis of the subclavian and axillary veins is probably more common than is generally realized. This report is based on 46 cases which we have observed during the past five years. In sixteen cases the thrombosis occurred as a complication of heart failure, in 10 it

was the result of effort or trauma, in 18 it was secondary to neoplasm, and in 2 it resulted from scar formation in the axilla.

A discussion of the general symptomatology is given, and variations peculiar to each of the main etiologic groups have been pointed out. The importance of measuring the venous pressure locally during exercise of the hand, as well as at rest, has been emphasized. The value of venograms in confirming the diagnosis and ascertaining the location of the venous obstruction and the extent of collateral circulation has been indicated.

Because of the high incidence of pulmonary embolism when the thrombosis complicates heart failure, it has been suggested that ligation of the subclavian vein be resorted to in these cases, in addition to the usual palliative measures.

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DISCUSSION

DR. B. JABLONS, Brooklyn, N. Y.—I should like to ask Dr. Veal whether there was any evidence in his cases of reflex involvement of the arterial system; in other words, whether there was spasm of the peripheral arteries.

DR. J. MURRAY STEELE, New York, N. Y.—It seems to me that this is an extraordinarily interesting phenomenon—the rise of pressure with exercise—and it explains very well something I saw three or four years ago. I did not know anything about this test at that time. While doing a venous pressure measurement, the patient felt a cramp in her arm and began to wiggle her hand. The water rose halfway to the top of the manometer, and now I know why.

I should like to make one other remark. Ten years ago a young boy was given arsphenamine without previously neutralizing the solution and he had an extensive thrombosis of the right axillary, subclavian, and brachial veins. He suffered numerous, successive pulmonary infarcts. Dr. Veal said he had not seen infection in any of the traumatic cases, but this one was extraordinary. There followed a series of seven or eight infarcts.

DR. IRVING S. WRIGHT, New York, N. Y.—There are two additional points which I believe are quite interesting. One was emphasized by Dr. Matas. It has a slightly different turn than that which Dr. Veal emphasized, not that he was in error, but there is an additional aspect. Dr. Veal emphasized the prolonged disability in these cases, and that is correct. But there is another factor which may mislead a man who is not experienced in taking care of axillary venous thrombosis.

Some of the patients with traumatic thrombosis apparently do recover entirely, but, in our experience, if they are allowed to go back to the same work or anything like the same work, involving the same type of motion, they may have a relapse.

Secondly, the question comes up as to the nature of a chemical thrombophlebitis. We have studied some of these cases, and, in a good many instances, it seemed to us that more than the chemical irritation of the solution was involved. In a number of instances, the needle actually penetrated the opposite wall of the vein, so that a small portion of the chemical substance was injected, not only into the lumen of the vein, but also into the wall of the vein, and therefore trauma was partially responsible for setting up an inflammatory process in the wall of the vein. This can be minimized by being certain that the needle is freely movable in the lumen of the vein before injecting.

I noticed from Dr. Veal's roentgenograms that, in at least one of the cases of chemical thrombosis, the vein was blocked all the way up, and not just at the subclavian, which would be additional evidence, in that case at least, that the thrombosing process extended from the site of the needle puncture into the subclavian.

DR. GEZA DE TAKATS, Chicago, Ill.—Will Dr. Veal discuss the treatment of this disease?

DR. A. WILBUR DURYEE, New York, N. Y.—I should like to ask Dr. Veal whether he thinks that, in any of these cases, the thrombosis was caused by pressure of the scalenus muscle.

I believe that, in certain instances, there may be actual mechanical obstruction of the subclavian by the scalenus. In these cases it seems logical, especially after the acute attack subsides, to do a scalenectomy to prevent further recurrence.

I should also like to ask Dr. Veal whether he uses heparin or any other anti-coagulant in cases of this kind.

DR. J. ROSS VEAL, Washington, D. C.—As to the question of Dr. Jablons, with regard to reflex arterial spasm, you may have noticed on the first slide that there was a note concerning cyanosis of the finger tips in the cold extremity. We feel that early in the stage of acute thrombosis there is reflex arterial spasm of the entire extremity. This, however, promptly disappears with proper treatment. Later, in the post-thrombophlebitic stage, we have not been able to demonstrate any real spasm or any other effect on the arterial system.

I think we would classify Dr. Steele's case of thrombosis after arsphenamine as one of chemical thrombosis, not mechanical. I was much interested to hear that pulmonary emboli do occur in these cases.

As to Dr. Wright's remarks about when the patient should be discharged after an attack of traumatic thrombosis, our experience has shown that we should not discharge a patient as cured unless his venous pressure has returned to normal limits on exercise. Very often a patient will come and say, "I am all well," and the swelling has disappeared, but, if he tries to go back to work, he will find that he is not able to do his work. And, once you discharge the patient, you put him in a bad position if he is not able to continue his work.

Also, in answer to Dr. Wright, I might say that, in the two cases of chemical thrombosis, the thrombosis seemed to begin at the point of the needle and extend all the way up to the subclavian.

Dr. de Takats has asked about the treatment of traumatic thrombosis. We simply prescribe rest, elevation of the arm, and application of heat. Dr. Ochsner, of New Orleans, has told me that he has used cervicodorsal sympathetic block with novocain, with prompt alleviation of the symptoms. However, we have not used that in our series of cases. We simply put the patient to bed, elevate the arm on pillows, and apply heat. We do allow these patients to move the wrist and elbow. We do not put them at complete rest.

Dr. Duryee's remarks about the scalenus are very important. The scalenus has not been investigated in these cases, and it might have some bearing on the etiology.

As to heparin, I have not had any experience with this drug in these cases of thrombosis of axillary and subclavian veins.

THE ELECTROCARDIOGRAM IN THE HYPERVENTILATION SYNDROME

WILLIAM PAUL THOMPSON, M.D., LOS ANGELES, CALIF.

HYPERVENTILATION is common in patients with anxiety neuroses. The symptoms produced by the unconscious act of overbreathing have recently been emphasized by Kerr, et al.,^{1, 2, 3} and by Soley and Shock,⁴ and include such common complaints and signs as weakness, dizziness, faintness, fainting, numbness and tingling about the mouth and in the hands and arms, palpitation, tachycardia, sighing respiration, muscular rigidity and cramps, hyperreflexia, tremulousness, and, in advanced cases, fully developed tetany, with carpopedal spasm and a positive Chvostek sign. That patients with the syndrome may have severe precordial pain with radiation to the arms, often suggesting the possibility of coronary artery occlusion, is well illustrated in the cases with which this report is concerned. That marked electrocardiographic abnormalities may also be produced, sometimes of a kind and degree suggestive of myocardial infarction, and much more marked than the simple depression of T previously described,^{5, 6, 7, 8} makes recognition of the syndrome of double importance.

That tetany may be produced in healthy persons by overventilation of the lungs has long been known. Kerr, et al.,^{1, 2, 3} have directed attention to the ease with which the hyperventilation test may be carried out, and the bizarre and often baffling complaints of patients when the syndrome has been reproduced to the satisfaction of both doctor and patient. We have applied the test to our patients and have been able to reproduce not only the symptoms but the electrocardiographic abnormalities as well.

MATERIAL AND METHOD

Twenty-five patients with the hyperventilation syndrome were observed during the past year at the Los Angeles County Hospital and in private practice.* These patients and a group of healthy hospital interns and resident physicians were studied. In an effort to reproduce the symptoms and electrocardiographic abnormalities, a hyperventilation test was applied in a number of instances to persons who were lying quietly and supine in bed. Forced overbreathing of room air as rapidly as possible and to the greatest extent to which the subject was capable

From the Los Angeles County Hospital and the Department of Medicine of the College of Medical Evangelists.

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was carried out for 90 seconds or until symptoms were produced. In the healthy subjects, it was sometimes necessary to continue the hyperventilation for three minutes in order to produce tetany. Electrocardiograms were taken before and immediately after the breathing and at frequent intervals thereafter until symptoms had disappeared and the electrocardiogram had returned to its original form.

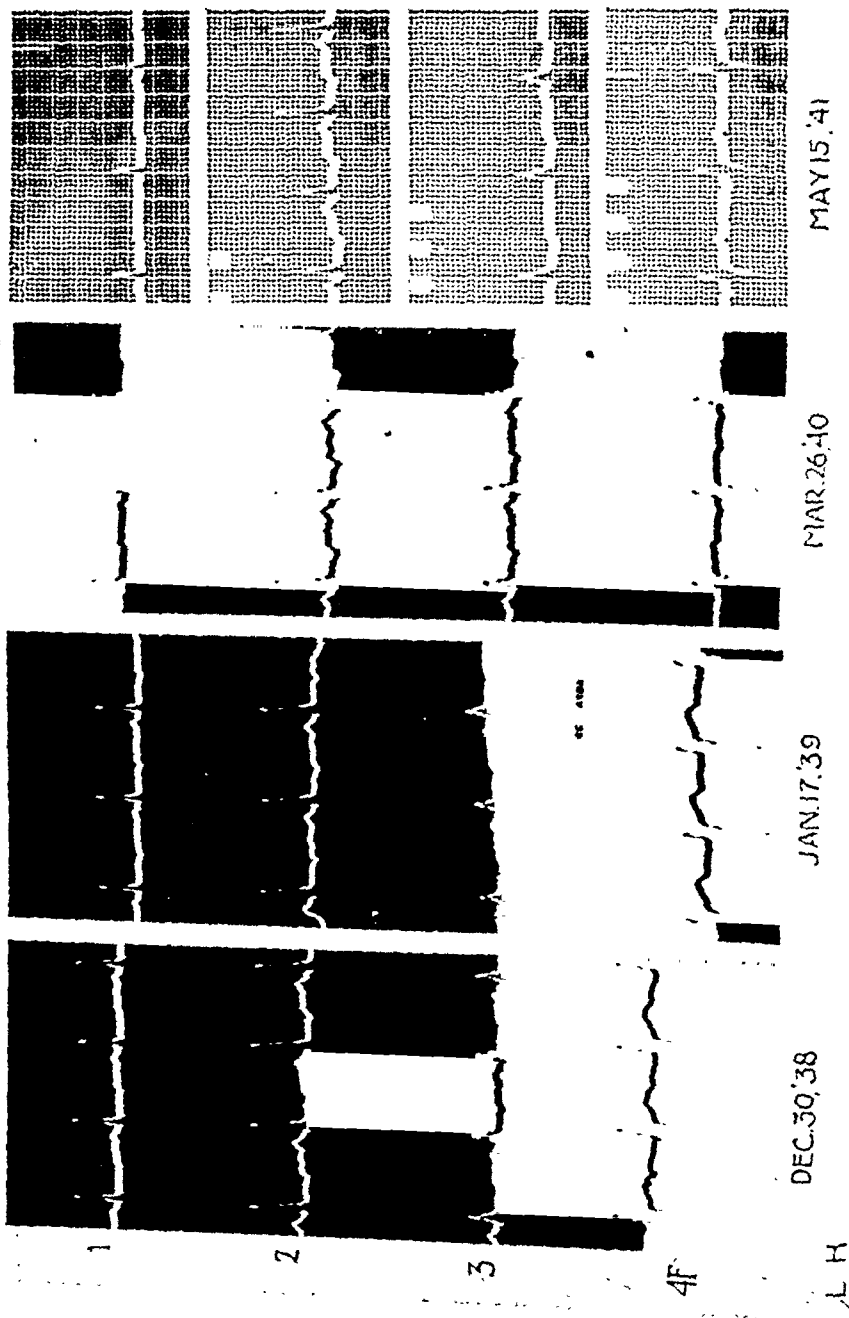


Fig. 1.—Case 1. Hyperventilation syndrome and normal heart. Electrocardiograms taken during the two and one-half years of frequent symptoms.

In a number of instances the carbon dioxide combining power and pH of the venous blood were measured, using a modified Van Slyke bicarbonate titration method and the Beckman pH meter. Hyperventilation with a mixture of 5 per cent carbon dioxide and 95 per cent oxygen was carried out in one normal subject.

The influence on the electrocardiogram of the increase in cardiac rate induced by the hyperventilation exercise was studied subsequently in a few resting subjects after inhalation of amyl nitrite or the intravenous injection of atropine sulphate.

OBSERVATIONS

On Patients with Normal Hearts and the Hyperventilation Syndrome.—Our attention was first directed to the hyperventilation syndrome as a cause of marked electrocardiographic abnormalities by Case

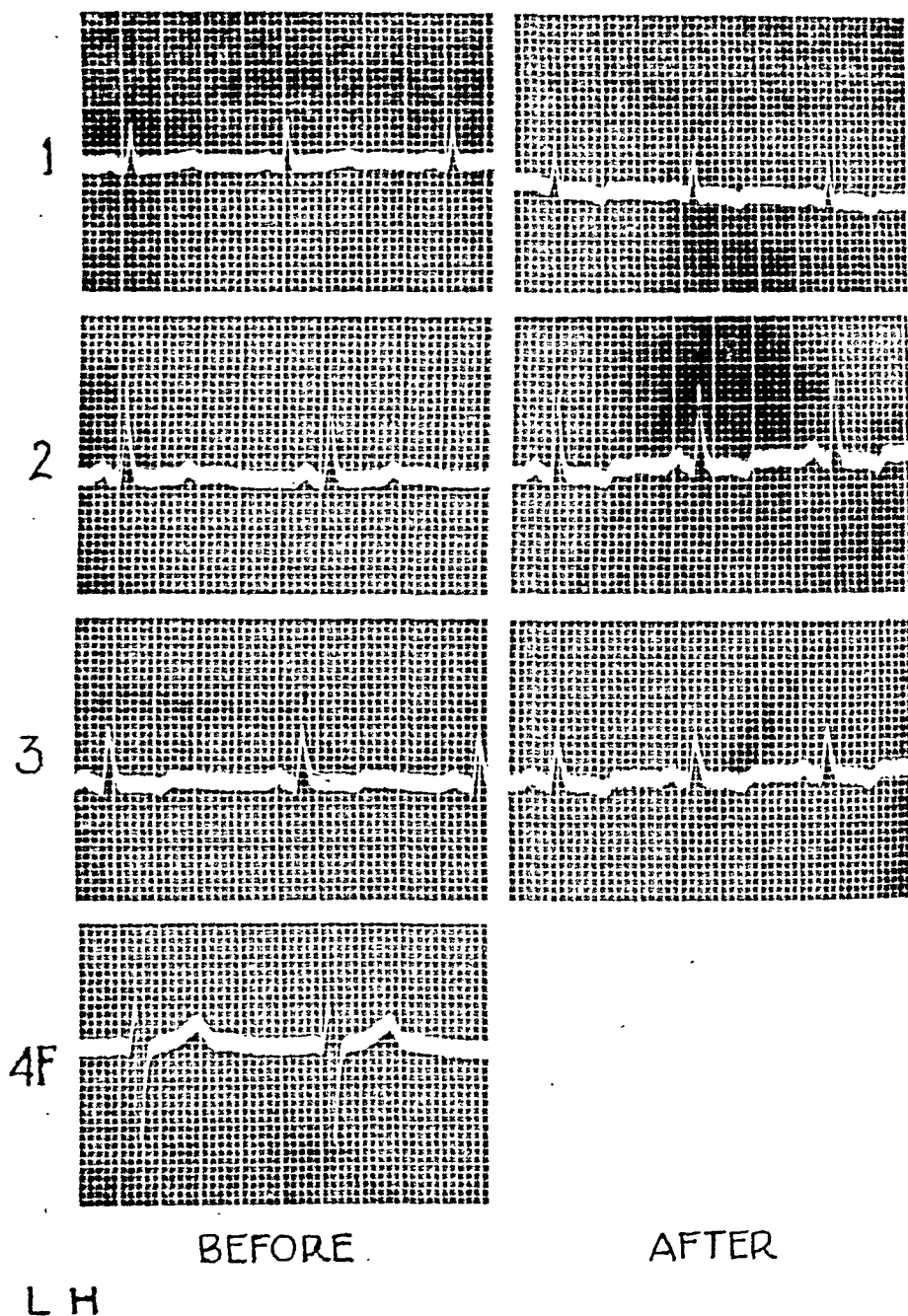


Fig. 2.—Case 1. Hyperventilation syndrome and normal heart. Patient at ease and free of symptoms. Electrocardiograms made before and after forced voluntary hyperventilation for 75 seconds. The T-wave inversion shown in Fig. 1 is reproduced.

1, that of a patient who was long considered elsewhere to have coronary artery occlusion and myocardial infarction. His series of electrocardiograms is reproduced in Fig. 1, and those taken immediately before and after the hyperventilation test are shown in Fig. 2.

CASE 1.—L. H., a man, aged 34 years, was an electric lineman. Two and one-half years before we saw this man he sustained an electric shock which burned his finger and caused momentary difficulty in getting away from the wire. He was weak thereafter but finished the day's work. The next three days he had soreness over the anterior part of the chest, and one month later had the first of a long series of attacks consisting of difficulty in breathing, dizziness, black vision, extreme faintness, weakness, palpitation, tremulousness, and pain across the chest. He thought he had heart trouble, but doctors told him he was nervous. Finally he was hospitalized for study. All tests were negative until "finally an electrocardiogram was taken, and they found out what the trouble was." A diagnosis of coronary occlusion and myocardial infarction was made; he was instructed to rest a great deal, and was finally given work as a bill collector. He disliked his new work intensely. The symptoms became worse, he was forced to be idle much of the time, and spent several long periods in hospitals.

Examination revealed much nervousness at first, but he was at ease later. The hands were cold and clammy. The heart was normal. The blood pressure was 128/86. The lungs were normal. The liver was not enlarged, and there was no edema. A slight, coarse tremor was present in the hands, and the tendon reflexes were moderately hyperactive.

Electrocardiograms taken over a period of two and one-half years were submitted, and are reproduced in Fig. 1. He stated that he had always been frightened while the tracings were being made. His new electrocardiogram, taken while he was entirely at ease, is shown in the left hand column of Fig. 2.

A *hyperventilation test*, consisting of forced overbreathing for seventy-five seconds, reproduced the symptoms of which he complained and the electrocardiographic abnormalities (Fig. 2). Symptoms produced by the test included precordial pain, dizziness, faintness, weakness, numbness, tingling, and tremulousness. A later hyperventilation test, when he was free of symptoms and the CO₂ combining power was 54 volumes per cent, again reproduced the symptoms and electrocardiographic abnormalities. The blood pH changed from 7.36 to 7.43.

The second case is notable with respect to the severity of the symptoms and the extreme inversion of the T waves in all leads (Fig. 3). Since the anxiety neurosis was firmly imbedded in this man, great difficulty was experienced in finding an opportunity to study him while he was free of symptoms and his electrocardiogram was relatively normal. Because his mornings were his best time, repeated visits were made early, with the result shown in the control in Fig. 4. The hyperventilation test reproduced his symptoms with great severity, and the electrocardiographic changes in part. During recovery the result of overcompensation is seen, with T waves taller than in the control.

CASE 2.—W. A. G., a man, aged 51 years, was a carpenter. (L.A.C.H. PF 746-616). For six months he had had almost daily attacks of severe burning, tearing, racking pain across the anterior part of the chest, radiating to the arms, neck, and back, together with great respiratory distress, orthopnea, dizziness, spots before the

eyes, cold sweat, nausea, fear, numbness and tingling, palpitation, and tremulousness. He had been hospitalized elsewhere for most of the six months and had been given much morphine. It was recorded in his progress notes that "the incidence of coronary occlusion in this patient seems to be increasing."

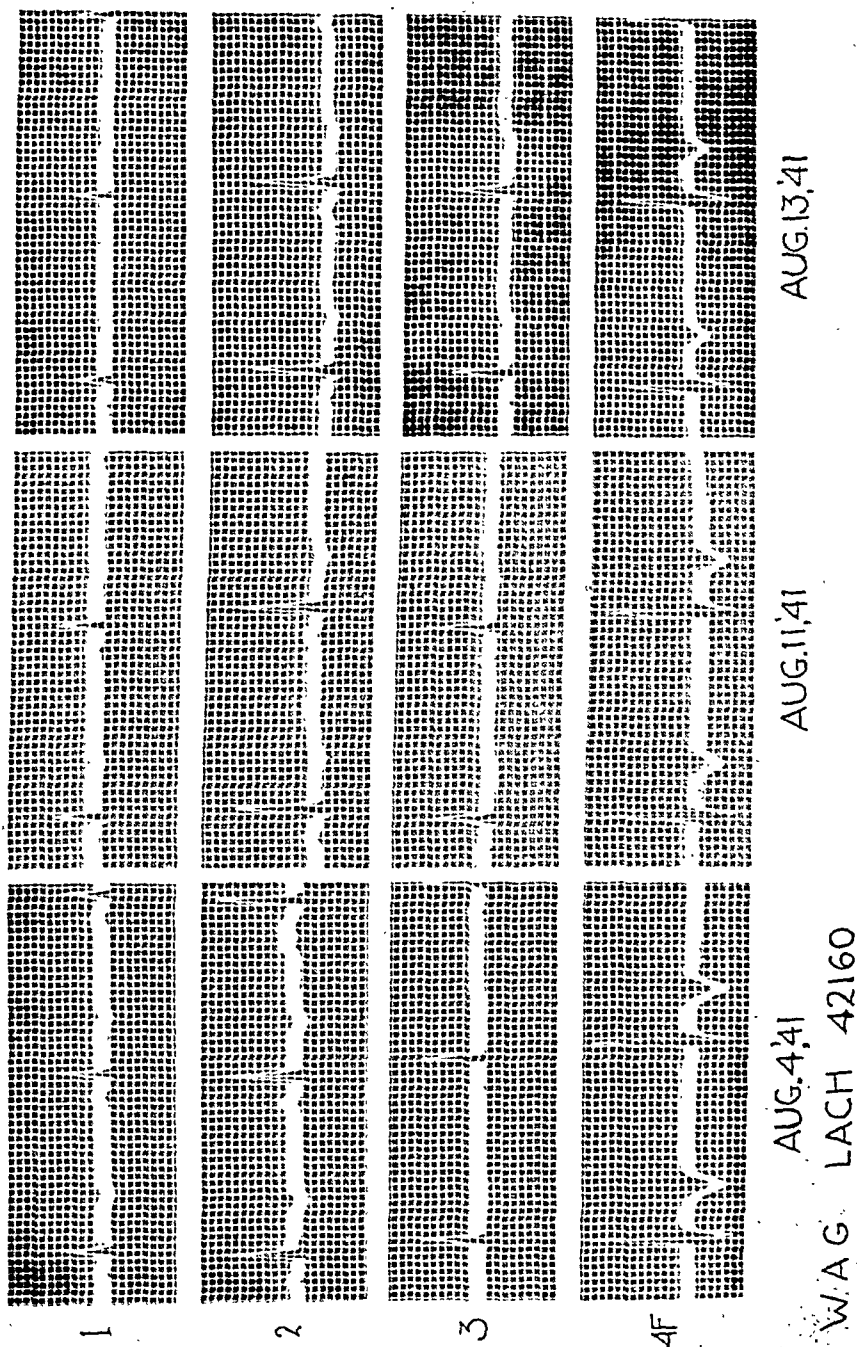


Fig. 3.—Case 2. Hyperventilation syndrome and normal heart. Electrocardiograms taken during period of frequent and severe symptoms.

Examination revealed frequent sighing respiration. Otherwise there was nothing abnormal. The heart was normal. The blood pressure was 106/62. No congestion of the lungs, veins, or liver was present.

Laboratory Data.—The hemoglobin was 110 per cent, the erythrocyte count, 5,560,000, and the leucocyte count, 7,300, with 76 per cent polymorphonuclear neutro-

philes. The corrected sedimentation rate (Wintrobe) was 36 and 19 mm. in one hour on two occasions (maximum normal, 9 mm.). The carbon dioxide combining power and blood pH were not measured.

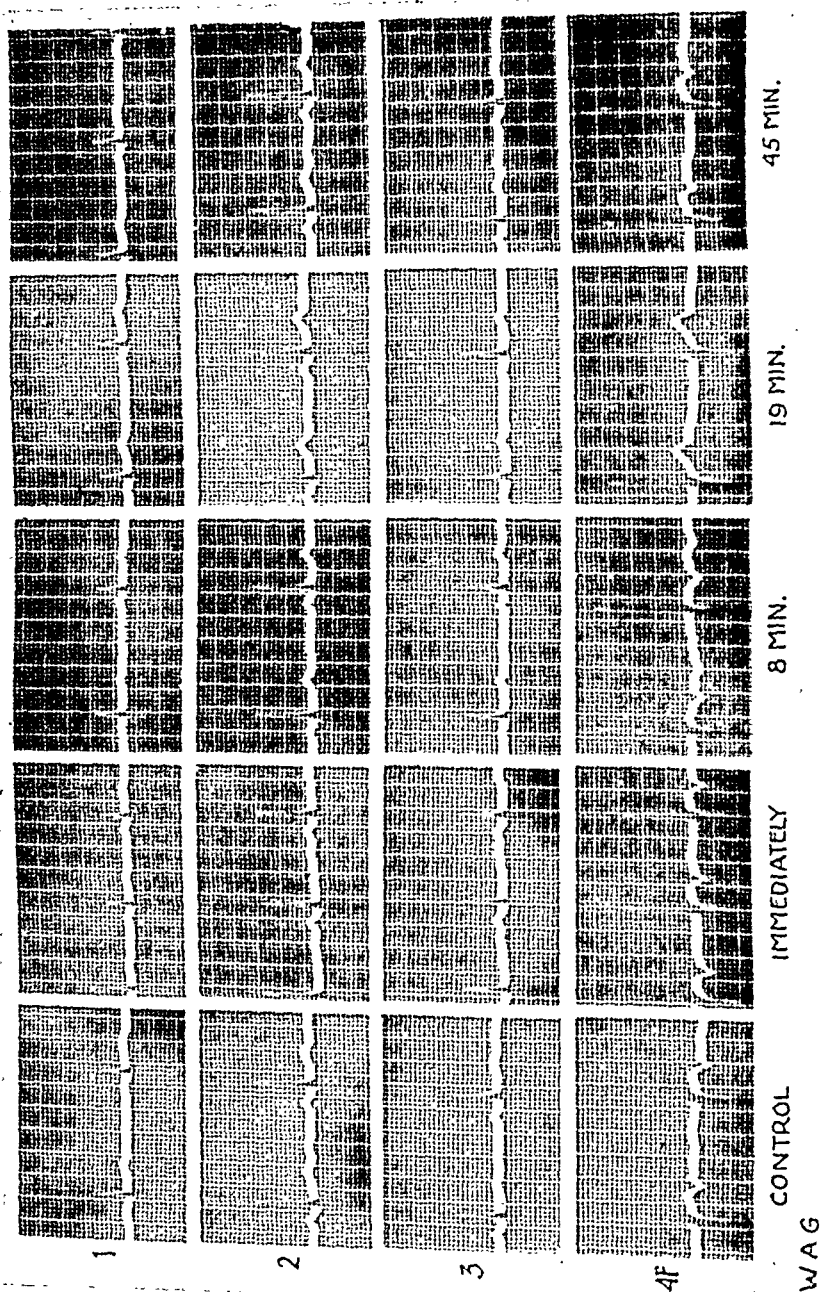


Fig. 4.—Case 2. Hyperventilation syndrome and normal heart. Control electrocardiogram made early on morning of Aug. 30, 1941, when symptoms were largely absent. Tracing taken immediately after forced voluntary hyper-ventilation for 30 seconds shows inversion of T₁ and T₂. Tracing taken 19 minutes after hyperventilation, during recovery, shows T waves taller than in control and an upright T in 4F. Tracings taken 45 minutes after hyperventilation, while patient was nervous and sighing, shows return of control configuration.

Electrocardiograms showed late inversion of T in all leads (Fig. 3). During his previous hospitalization, four electrocardiograms had been made (not reproduced here), the first two of which were similar to those reproduced; the third and fourth showed upright and normally tall T waves in Leads 1, 2, and 3, with diphasic T waves in the chest leads. There were no abnormalities of QRS.

A *hyperventilation test*, done after many early morning visits in an attempt to study the patient at a favorable time, when he was free of symptoms and his electrocardiogram relatively normal, produced, after 30 seconds of forced overbreathing, marked carpopedal spasm, a positive Chvostek sign, tremulousness, crushing pain over the heart, and inability to stop hyperventilating. Fig. 4 shows the control electrocardiogram and those taken after the overbreathing. Inversion of T in leads 2 and 3 occurred immediately afterward. Of especial interest is the tracing taken 19 minutes after the hyperventilation, during the recovery period, in which the T waves throughout are taller than in the control, and T in Lead IV F is entirely upright.

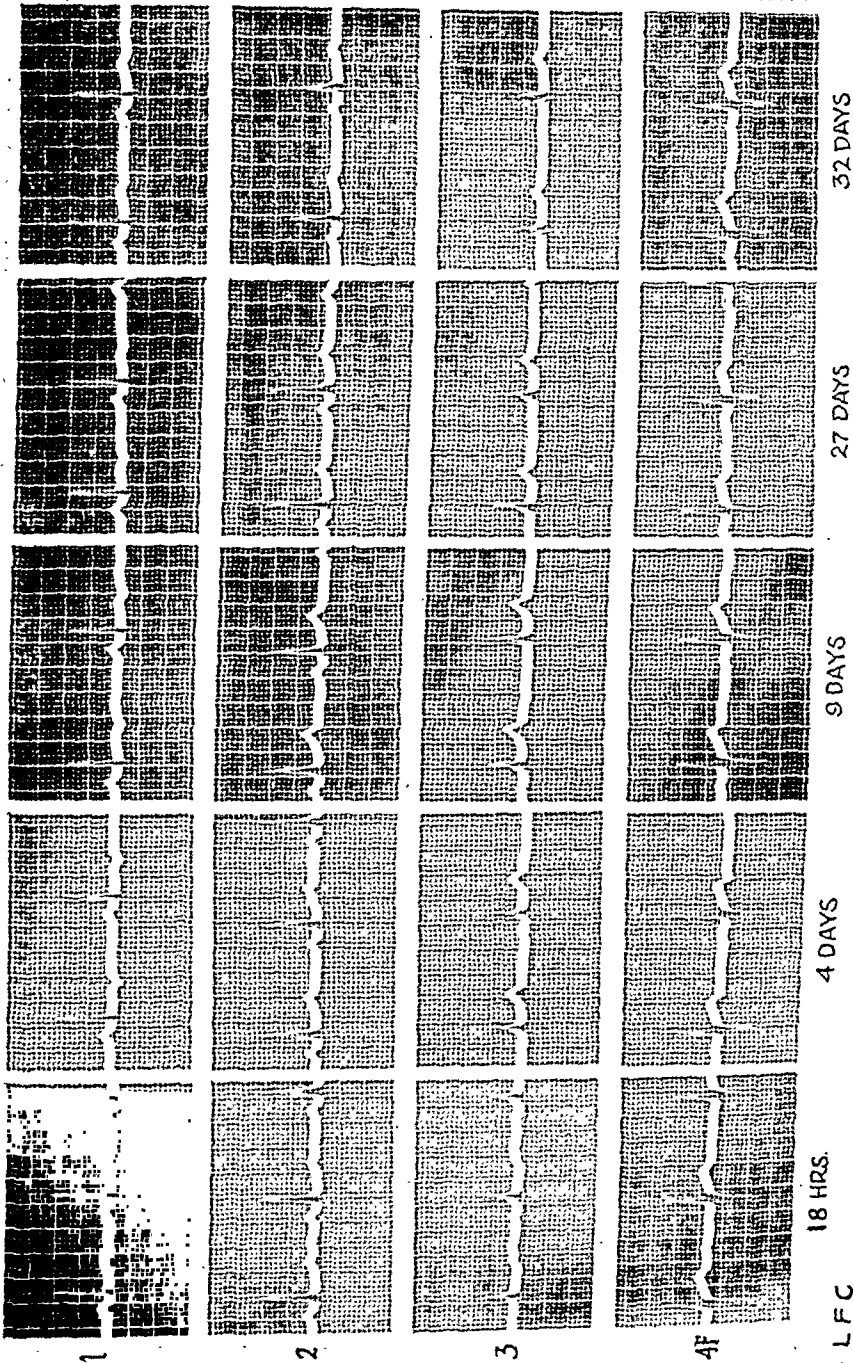


Fig. 5.—Case 3. Hyperventilation syndrome and normal heart. Serial electrocardiograms, starting 18 hours after precordial pain which was originally attributed to coronary occlusion. Note absence of QRS abnormalities.

The third patient appeared at first to have had acute coronary artery occlusion, but the correct diagnosis became apparent later, when his course was observed. His T-wave inversion (Fig. 5) was originally regarded as consistent with anterior myocardial infarction, although not entirely confirmatory, but S-T deviation and QRS changes did not appear. The tracing had returned to normal on the 32nd day, and, on the 33rd day, a hyperventilation test was performed. Although the overbreathing was carried out very poorly, a period of involuntary sighing was initiated, and his previous T-wave abnormality was reproduced (Fig. 6).

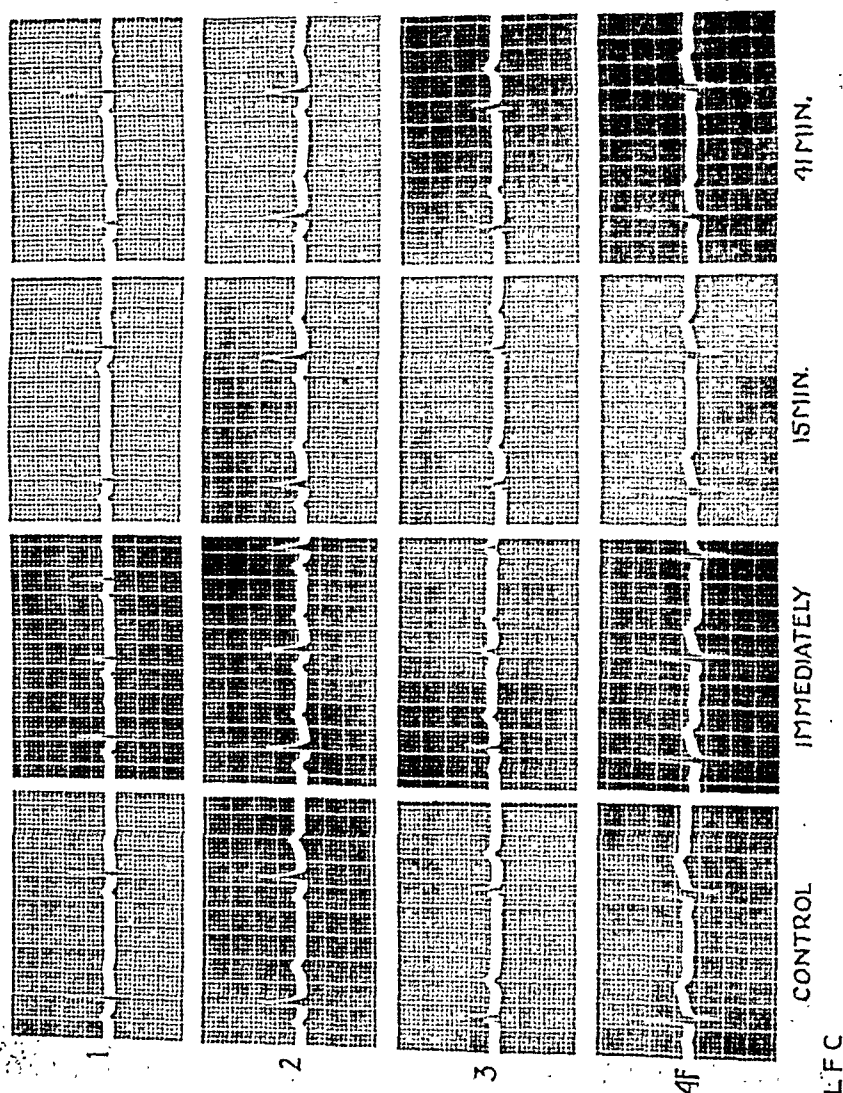


Fig. 6.—Case 3. Control electrocardiogram and hyperventilation test on thirty-third day of illness. Voluntary overbreathing poorly executed, but followed by much sighing, resulting in inversion of T, 11 minutes after start of the test.

CASE 3.—L. F. C., a man, aged 38 years, was a shipping clerk. Late in the afternoon of the day before admission to the hospital the patient ate unwisely, slept 5 hours, then awakened in a nightmare. He felt unable to get thoroughly awake,

and noted a peculiar shortness of breath, numbness and tingling, and pain over the lower part of the sternum and in the left shoulder. The pain varied in intensity in wave-like form, and became very severe, as if he "had been kicked by a horse." He was unable to breathe deeply without increasing the pain. He became weak, the whole left arm ached, and he perspired and was nauseated. The symptoms continued until he was examined 18 hours later.

Examination revealed great apprehension and slight pallor. The heart was normal. The blood pressure was 150/90. There was no congestion. The tendon reflexes were hyperactive.

Course.—After examination, 20 c.c. of aminophyllin were given into the left antecubital vein. During the injection of the solution he complained of severe pain in the left arm, with inability to move the extremity. He perspired, began to overbreathe, and complained of dizziness and numbness and tingling in the right hand. Inhalation of a carbon dioxide-oxygen mixture brought relief of all symptoms except the pain in the arm. He was unable to move the arm for several days, and was afraid to change his position in bed. He complained that his heart felt "big," and developed an extreme cardiac neurosis. His temperature was normal throughout.

Laboratory Data.—The hemoglobin was 100 per cent, the erythrocyte count, 5,240,000, and the leucocyte count, 17,800. Differential leucocyte count: neutrophils, 66.5 per cent; lymphocytes, 28.5 per cent; monocytes, 3 per cent; eosinophiles, 2 per cent. The leucocyte count gradually fell to normal by the twentieth day. The sedimentation rate was not done until the twentieth day, when a fall of 12 mm. occurred in 88 minutes (normal, 12 mm. in 120 minutes, Linzenmeier).

The *electrocardiogram* was normal at first, then late inversion of T_1 appeared and persisted until the thirty-second day (Fig. 5). Abnormalities of QRS were not observed.

A *hyperventilation test*, performed on the thirty-third day, was preceded by apprehension, sighing, and tingling in the chest and shoulders. The overbreathing was poorly performed, but set off involuntary sighing and resulted in inversion of T_1 after 41 minutes (Fig. 6). After the test he developed tremulousness and a sense of weight over the heart.

Changes in the QRS complexes have been inconspicuous in our cases.

In but a single case has the QRS change been such as to suggest the possibility of myocardial infarction, and was even then limited to the chest lead. In this instance a well-marked abnormality in QRS in Lead 4F followed a painful seizure diagnosed elsewhere as acute myocardial infarction, with return to normal by the time we were consulted. The hyperventilation test, performed because of our uncertainty about the question of infarction, produced variations in QRS in Lead 4F of a similar kind, but less in degree than those which had occurred spontaneously (Figs. 7 and 8).

CASE 4.—Mrs. L. D. W., aged 54 years, was a housewife. The history was one of a lifetime of nervousness, easy fainting, and frequent sighing respiration. Years previously her only pregnancy was terminated because she was ill with cramps and spasms in the muscles of the extremities. Twelve years before our examination her menses ceased. Thereafter she had had much nervousness, weeping, hot flashes, sudden perspiration, throbbing in the head, dizziness, exhaustion, faintness, and fainting. Injection therapy for the menopause had never been given because of her fear of the needle. Oral therapy had not been given with regularity or persistence. She had not improved as time passed, and her husband became intolerant of her invalidism, thus aggravating it.

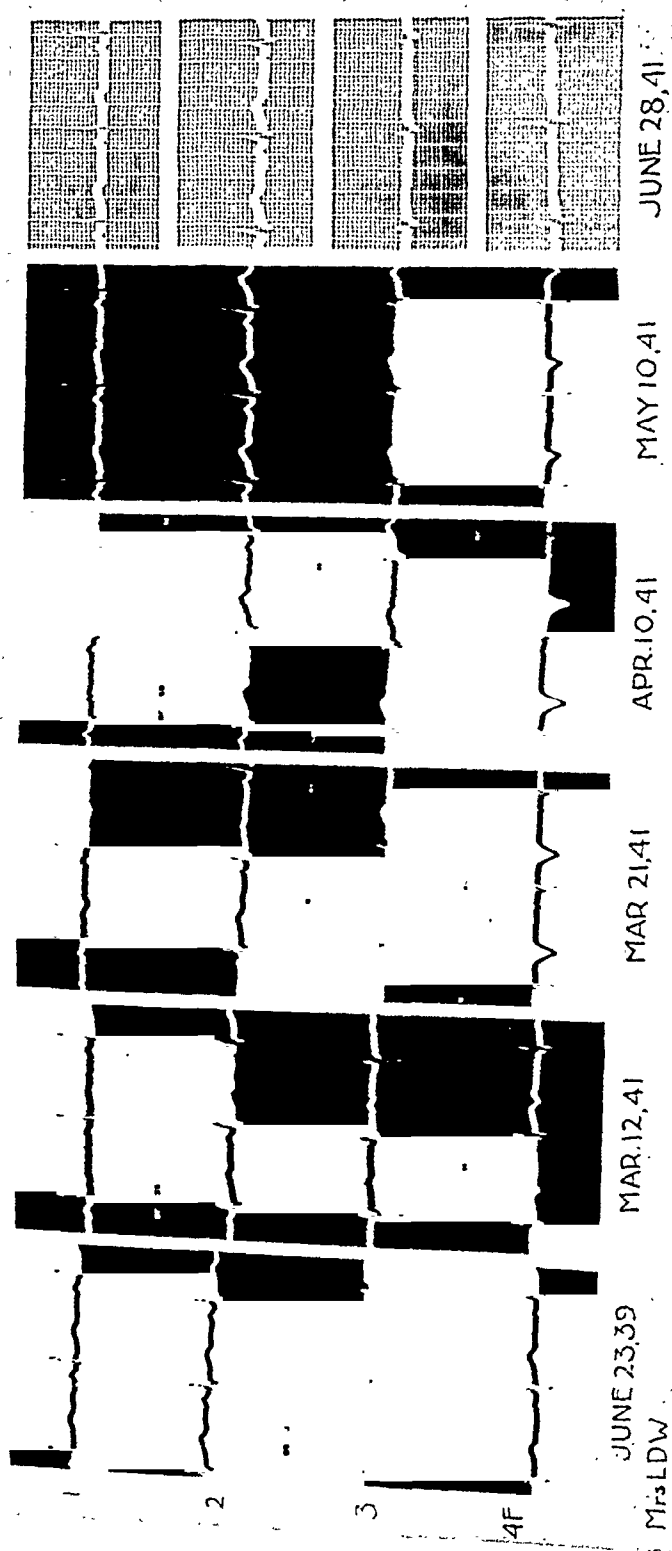


Fig. 7.—Case 4. Hyperventilation syndrome and normal heart. First electrocardiogram serves as control for serial changes after attacks of severe precordial pain and fainting, starting March 5, 1941. Note the development of W-shaped QRS in Lead 4F.

Two years before we saw her she experienced marked respiratory difficulty, in the form of a nervous catch in her breath, gasping, and extreme exhaustion. Such attacks were frequent, sometimes lasting a whole day. Many doctors were consulted, and wide differences in opinion were expressed. An electrocardiogram, taken two years before we saw her, was normal (Fig. 7, first column).

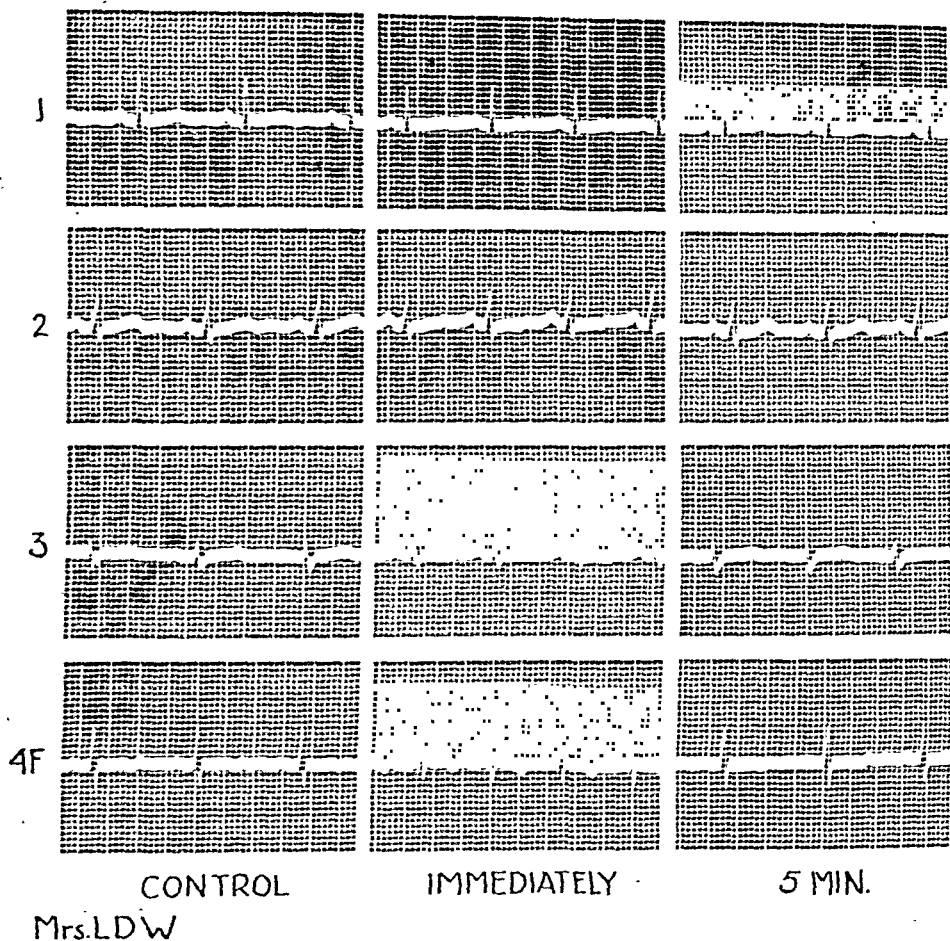


Fig. 8.—Case 4. Hyperventilation test on July 1, 1941, was preceded by yawning and lowering of T, as compared to last electrocardiogram in Fig. 7. Immediately after forced voluntary hyperventilation for 75 seconds the T waves became lower and QRS in Lead 4F became triphasic.

On March 5, 1941, three and two-thirds months before we saw her, she experienced a severe, tight pain about the left breast and xiphoid, rising to the throat, where a spasm followed. She had much difficulty in breathing, and fainted. Seven more such attacks followed in the next six days. On March 12 she consulted a physician who diagnosed heart disease. The electrocardiogram taken on that day and those taken subsequently are reproduced in Fig. 7, ending with the tracing made the day we first saw her (June 28, 1941). Hospitalization was advised on March 12, but refused. She spent most of her time in bed at home thereafter, and was never free of some kind or another of chest pain, usually in the form of a dull ache about the left breast and axilla, often interrupted by sharp, momentary, cutting sensations. Precordial tenderness was marked, and faintness was frequent. There was no fever. She developed much fear of sudden death.

Examination revealed a weeping, dejected woman who appeared otherwise healthy. The heart was normal in size, the sounds were normal, and there were no murmurs.

The blood pressure was 112/72. The lungs were normal, the jugulars were not distended, the liver was not enlarged, and edema was absent. The tendon reflexes were normal. Fluoroscopic and orthodiagraphic examination showed a heart of normal size and shape; its position and pulsation were normal. The lungs were negative.

Three days after her initial visit she returned for further study. A *hyperventilation test* was preceded by considerable yawning. The control tracing (Fig. 8) showed slight inversion of T in Lead 4F; this had been absent 3 days before, and was presumably caused by the overbreathing attending the yawning. After 75 seconds of moderately forced voluntary hyperventilation, a change in QRS in Lead 4F appeared; it resembled in kind but not in degree the changes previously observed. The small Q in Lead 4F disappeared after a dozen cycles. Lowering of T in the standard leads and deeper inversion of T in the chest lead were also noted, with return to the control conformation in five minutes. Because of the extreme anxiety of the patient, hyperventilation was not continued to the point of carpopedal spasm, tremulousness, or a positive Chvostek sign.

The next patient's electrocardiogram was normal when she was seen by us, but she had previously been told that she might have pericarditis because her T waves were low. Her hyperventilation test produced striking electrocardiographic changes, consisting of S-T depression, with lowering and inversion of T (Fig. 9), rather than the late type of inversion of T which occurred in the first four cases. This type of alteration has been more common in our cases than the more striking late inversion, and resembles the changes which occur when the test is applied to healthy subjects (Fig. 10). It is quite likely that the symptomless state of this patient at the time of her test caused her to behave like a normal person.

CASE 5.—Mrs. H. M. H., aged 38 years, was a housewife. For fifteen years the patient had had many attacks of palpitation, tachycardia, gasping respiration, dizziness, apprehension, weakness, nausea, and a clutching sensation in the left anterior axillary line. She felt cold and tremulous during the attacks. Her anxiety had been much increased when a physician expressed his suspicion that her low T waves were the result of pericarditis.

Examination was entirely negative. Sighing and objective evidence of apprehension were absent at the time of her visit. The heart was normal in size, the sounds were normal, and there were no murmurs. The blood pressure was 114/80. No congestion was found. The tendon reflexes were moderately hyperactive. Fluoroscopic examination revealed a heart of normal size, pulsating normally, and normal lungs.

A *hyperventilation test*, carried out when she was free of symptoms and at ease, was continued for 85 seconds, and resulted not only in conspicuous lowering of T in leads 1 and 2, but also in S-T depression in leads 2, 3, and 4F, and in inversion of T in leads 3 and 4F (Fig. 9). The induced symptoms and signs included dizziness, blackness before the eyes, headache, numbness and tingling in hands, a sense of dead weight in the arms, pounding of the heart, slight nausea, tremulousness, and a positive Chvostek sign. Carpopedal spasm did not appear.

Observations on Patients with Heart Disease and the Hyperventilation Syndrome.—Several patients with heart disease, who have had anxiety neuroses and the hyperventilation syndrome, have been observed. These only serve to emphasize that a diagnosis of hyperventilation

syndrome does not preclude the possibility of concomitant heart disease. One such patient, an Army colonel, 52 years of age, had acute coronary artery occlusion, with posterior myocardial infarction, which was typical in all respects, including serial electrocardiographic changes, but his symptoms after subsidence of the initial pain were those of hyperventilation, and included nervousness, sighing respiration, muscular cramps,

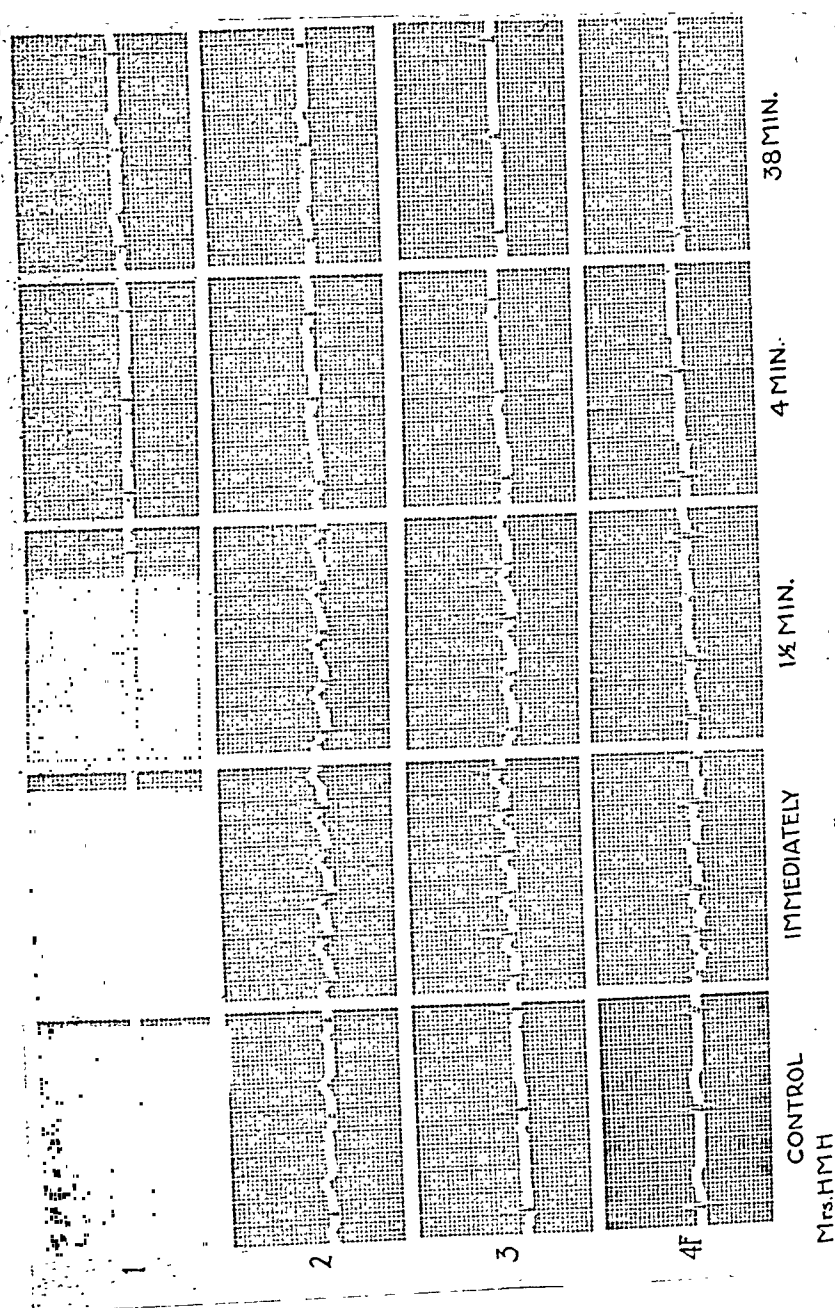


Fig. 9.—Case 5. Hyperventilation syndrome with normal heart. No symptoms preceding test. Immediately after forced voluntary hyperventilation for 85 seconds, depression of S-T, lowering of T, and inversion of T occurred. This response resembles that of healthy subjects, but is more marked.

light-headedness, and numbness and tingling of the hands, arms, and face. He became a disciplinary problem, criticised the medical officers, and frequently got himself and others into trouble. A hyperventilation test has not been carried out because his electrocardiogram still shows prominent Q waves and deep, late inversion of T in Leads 2 and 3.

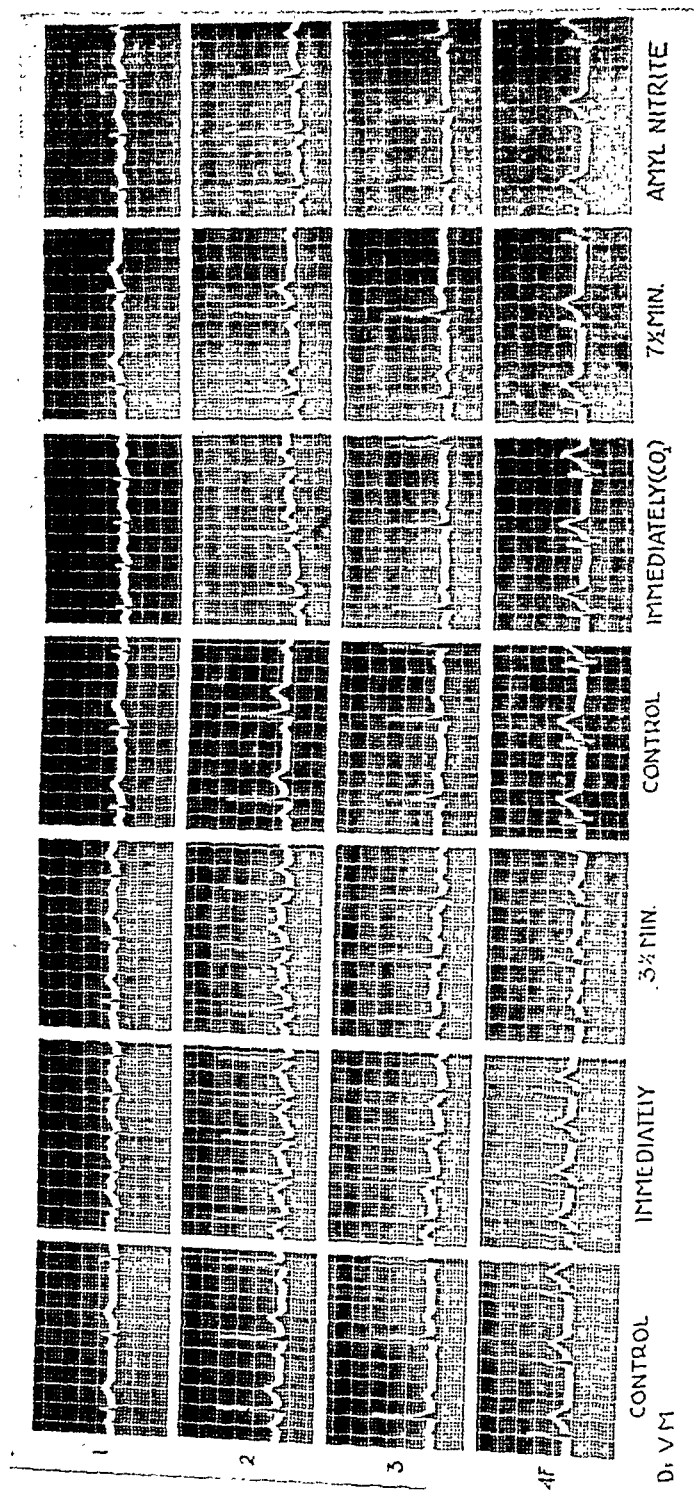


Fig. 10.—Healthy young doctor without the hyperventilation syndrome. First 3 columns illustrate effect of forced voluntary hyperventilation for 3 minutes. Immediately after the overbreathing, S-T depression and T flattening are seen. Fourth column represents control, a week later. Fifth column illustrates effect of hyperventilation for 3 minutes of a mixture of carbon dioxide and oxygen. Last column illustrates effect of tachycardia induced by inhalation of amyl nitrite.

Observations on Healthy Subjects.—The hyperventilation test was applied to six healthy young doctors. Overbreathing was continued to the point of carpopedal spasm in five of them, for which about two and one-half to three minutes were required. In all on whom the test was carried far enough, electrocardiographic changes were observed. These consisted of acceleration of rate, depression of S-T segments, and lowering or flattening of T waves in any or all leads. The most conspicuous changes were seen in Leads 2 and 3. In the first three columns of Fig. 10 a typical result is reproduced. Late inversion of T was not observed in any of the healthy subjects. The carbon dioxide combining power was normal in all, ranging between 56 and 64 volumes per cent. The pH of the venous blood before the test was normal in all, ranging from 7.35 to 7.38, with increases immediately after hyperventilation of 0.06 to 0.12; the maximum figure was 7.52. In addition to measurement of the control CO₂ combining power, measurements were at first made on blood taken after the hyperventilation, but the changes were insignificant during the short period of the tests, and the practice was discontinued.

CAUSE OF THE T-WAVE ABNORMALITIES

Overbreathing washes excessive amounts of CO₂ from the lungs and secondarily from the blood, resulting in the loss of acid ions and a shift of the blood pH in the direction of alkalinity. In our healthy subjects the maximum alkaline shift occurred at the time when the electrocardiographic abnormalities were at their maximum. The assumption is that the abnormalities are the result of alkalosis. Similar alkaline shifts have been observed during the test in some of our patients with the hyperventilation syndrome, however, without change in the electrocardiogram. In addition, well-marked, spontaneous, T-wave inversion has occurred in some of our patients at times when the pH of the venous blood was normal. These observations raise some question whether a rise in pH is the crucial factor in determining electrocardiographic change.

When CO₂ is exhaled in excessive amounts, a state of uncompensated CO₂ deficit follows. If this deficit is continued for a sufficient time (longer than 3 minutes, or less, in our tests), base is excreted in the urine, an alkaline urine is produced, and the CO₂ combining power of the blood is reduced. A state of compensated CO₂ deficit is thus produced, and the pH returns to normal. Three of our patients were admitted with CO₂ combining powers of 35, 35, and 36 volumes per cent, respectively. Two of these patients had well-marked T-wave inversion when the combining power was low, and one of them exhibited only minimal depression of S-T in Leads 1 and 4F. Two of them were studied later, when the combining power had risen to 48 volumes per cent, at which time the electrocardiograms were unchanged. Unfortunately, some of our patients with the most striking electrocardio-

graphic abnormalities were observed early in the course of the study, before chemical observations were being included. At present it appears that neither the degree of alkaline shift nor the extent of lowering of the CO_2 combining power is the sole factor in determining the kind or magnitude of the S-T and T changes. Much more study is necessary before this is established, however. Even if one of these factors is subsequently found to be the important one, the exact mechanism by which it operates in altering the electrocardiogram must still be explained.

Barker, et al.,⁸ have shown that the hyperventilation of air from a large dead air space, by means of which the removal of excessive amounts of CO_2 from the lungs and blood may be prevented, will result in no tetany and no change in the electrocardiogram. Soley and Shock⁴ relieved the symptoms of their patients by the administration of atmospheres containing 2 to 5 per cent of CO_2 . Fig. 10 illustrates a similar experiment on one of our healthy subjects. In the fourth column is the control tracing, made a week after the hyperventilation test illustrated in the first three columns. Forced hyperventilation with a mixture of 5 per cent CO_2 and 95 per cent oxygen was carried on for 3 minutes. The experiment was not conducted too satisfactorily because the subject breathed through a loose-fitting face mask which allowed an insufficient flow of about 12 liters of gas mixture per minute. The experiment led to slight tetany (much less than during the previous experiment), with a pH change from 7.40 to 7.48, which was again much less than before. S-T depression did not occur, although the T waves in the standard leads did become slightly lower. It is reasonable to assume that, had the experiment been conducted under more ideal circumstances, both the tetany and T-wave changes would have been absent.

In the normal subjects and in many of the patients who were tested after recovery from the syndrome, S-T and T alterations were never observed in the absence of appreciable increases in heart rate. In these subjects, depression of S-T, especially in Leads 2 and 3, was more conspicuous than flattening of T, and late inversion of T was never observed. A good example of this is illustrated in Fig. 10. To study the effect of acceleration of the heart rate without hyperventilation, we administered amyl nitrite by inhalation to two subjects, and 2.6 mg. ($\frac{1}{25}$ grain) of atropine sulphate by vein to another. The resulting changes were similar to those produced by hyperventilation. In Fig. 10 the effect of amyl nitrite on a healthy subject is illustrated in the last column. Although the acceleration was not as great as that after hyperventilation, the result is obviously similar.

Acceleration of rate is not the cause of the conspicuous late inversion of T shown in Figs. 1, 3, 5, and 7, which illustrate cases in which T-wave negativity appeared spontaneously. It is wholly possible that acceleration is the cause of the S-T depressions, but not of the late inversion of T.

DISCUSSION

It is evident that patients with the hyperventilation syndrome at times show conspicuous, late inversion of the T waves. Others show S-T depression and pronounced lowering of T, possibly through the mediation of acceleration of rate. Rarely, QRS abnormalities may be observed.

The ramifications of this are considerable in cardiovascular medicine, for the syndrome often includes severe precordial pain which suggests the possibility of coronary artery occlusion. The symptoms, plus the electrocardiographic abnormalities, must make the physician careful not to be led to an erroneous diagnosis of myocardial infarction, with its resulting accentuation of the already severe anxiety neurosis. Although the electrocardiographic abnormalities are distinctly not those of myocardial infarction, they have nevertheless frequently been so interpreted in the cases we have seen, and we ourselves have made the error.

The Possibility of Heart Disease.—The possibility that our patients, especially those with late inversion of T, actually suffered minor infarctions which did not produce ordinary patterns, and that the hyperventilation syndrome was simply an added factor, cannot be lightly dismissed. Barach et al.,⁹ have cited the work of others^{10, 11, 12, 13, 14} and pointed out that alkalosis produces vasoconstriction. They have shown, also, that the experimental inhalation of low-oxygen atmospheres is attended by hyperventilation and an alkaline shift. When patients with the anginal syndrome are subjected to low-oxygen atmospheres and develop S-T and T deviations, it is possible that the deviations are due to vasoconstriction produced by alkalosis. Such a mechanism, it must be admitted, could operate in our cases; the vasoconstriction might reduce the blood supply to the myocardium sufficiently to reproduce the spontaneous electrocardiographic patterns. It is our belief, however, that our patients have normal hearts. We have no final proof that the hearts are structurally normal, for all of the patients are still living. Against the presence of coronary artery disease are the relative youthfulness of most of them (the youngest who was thought not to have heart disease was 25 years old, the oldest, 62 years; average, 40.5 years), the fact that 10 are women, that none had hypertension, and that none had fever after spontaneous attacks.

Leukocytosis and an increase in the sedimentation rate were observed in two cases. Whether or not such changes can be produced by alkalosis is now under consideration.

Frequency of Electrocardiographic Abnormalities.—In only six of the 25 persons were all of the electrocardiograms normal. We suspect that most patients with the syndrome, if not all, will exhibit abnormalities if tracings are taken at the proper time. It is likely that changes would be conspicuous when the blood pH has been shifted

markedly toward alkalinity, still more conspicuous when an alkaline shift occurs in a patient who has already lost an appreciable amount of his alkali reserve, and entirely absent in a patient whose electrocardiogram is not taken until he has recovered from his symptoms and the dislocation of his acid-base balance. Case 1 is such an example: the control tracing in Fig. 2 was entirely normal (with the patient at ease), and all tracings which showed inversion of T were taken when he was frightened by the procedure (Fig. 1). It is further likely that the hyperventilation test will fail to reproduce electrocardiographic abnormalities in striking degree when recovery from the syndrome has been allowed to progress too far.

Hyperventilation in Other Conditions.—It is only reasonable that hyperventilation may be a factor in the genesis of symptoms in a wide variety of diseases when the element of anxiety is added. Such an example is the Army colonel, whose symptoms, after subsidence of the initial pain of coronary artery occlusion, were clearly those of anxiety and hyperventilation. Case 4 is that of a menopausal woman who suffered also from hyperventilation.

Scherf¹² has attributed S-T depression and T negativity to the menopause. His tracings were similar to ours, and returned to normal when estrogenic therapy relieved the symptoms of the menopause. It is not impossible that his electrocardiographic deviations were, in fact, the result of hyperventilation.

Graybiel, Starr, and White¹³ reported S-T and T changes after the inhalation of tobacco smoke. Their electrocardiograms are similar to ours. We have had the opportunity to observe them conduct one of their tests, during which the smoke of one to three cigarettes was inhaled as rapidly and deeply as possible. Hyperventilation may have been responsible for the electrocardiographic changes.

SUMMARY

1. Patients with anxiety neuroses and the hyperventilation syndrome frequently exhibit marked electrocardiographic abnormalities, consisting either of late inversion of T, or of S-T depression with marked lowering of T. Any or all leads may be involved. QRS changes have been observed in but a single case and were limited to Lead 4F.

2. The abnormalities disappear when recovery from the syndrome takes place, but may be reproduced by voluntary hyperventilation if recovery has not become too firmly established.

3. Evidence is presented to suggest that the abnormalities are the result of alkalosis, but certain discrepancies raise some question whether this is the sole factor.

4. Since severe precordial pain may be included in the syndrome, recognition of these marked electrocardiographic abnormalities assumes importance, lest they be attributed to infarction of the heart, with the result that the anxiety neurosis becomes worse.

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DISCUSSION

DR. FRANCIS L. CHAMBERLAIN, San Francisco, Calif.—Dr. Thompson has shown very well the changing electrocardiograms of nervous people with nervous hearts. However, it should be emphasized that there are mechanisms other than hyperventilation that may be responsible for electrocardiographic changes of this type. Dr. Paul White, Dr. Ashton Graybiel, Miss Ola Nagle and I have found that hyperventilation is one of several mechanisms.

Variation in the position of the diaphragm is of importance. Thus, deep inspiration or the sitting position lowers the diaphragm, and, in so doing, may invert T waves, especially in Leads 2 and 3.

Apprehensive persons often breathe during periods of excitement in such a way that their reserve air is greatly increased at the expense of their complementary air, thus lowering the diaphragm. This may be an important factor.

In some patients hyperventilation may similarly lower the diaphragm.

Autonomic nervous system imbalance also appears to result in T-wave abnormalities, as shown by the effect of epinephrine, atropine, ergotamine, and acetyl- β -methylcholine.

It is well to remember that hyperventilation may reverse T waves when the heart is abnormal. Two of our patients in the past three years, who had normal electrocardiograms which became abnormal with hyperventilation, both of them obviously patients who fitted into this so-called hyperventilation syndrome, have since died very suddenly, and the autopsies showed that death was the result of coronary disease.

Clinical Reports

TRICUSPID STENOSIS AND PULMONARY STENOSIS COMPLICATING CARCINOID OF THE INTESTINE WITH METASTASIS TO THE LIVER

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TRICUSPID stenosis is usually found in association with other cardiac lesions, particularly with valvular disease of the left side of the heart. As an isolated lesion it is considered a clinical curiosity, and in association with pulmonary stenosis it is even more uncommon.

Among the 194 collected cases of tricuspid stenosis of Leudet,¹ J. B. Herrick,² Griffith,³ W. W. Herrick,⁴ and Futeher,⁵ only three instances of tricuspid stenosis and pulmonic stenosis without involvement of the other valves were reported. In 1880, Osler⁶ presented a case. Cabot⁷ reviewed 33 cases of tricuspid stenosis in association with other valvular lesions. There were two cases of stenosis of the tricuspid and pulmonary valves. Castellanos and his associates⁸ have also described a case.

The clinical aspects and circulatory dynamics of tricuspid stenosis have been adequately described by Friedlander and Kerr,⁹ Altschule and Blumgart,¹⁰ Altschule and Budnitz,¹¹ and Kerr and Morrison.¹² In 34 cases of tricuspid stenosis the diagnosis has been made clinically.

Because of the rarity of the combination of tricuspid and pulmonary stenosis without other valvular lesions, and the difficulties encountered in diagnosis, it is felt that this case is worthy of record.

CASE REPORT

B. K., a 44-year-old woman, married for 23 years, who had had five full-term pregnancies without any untoward manifestations, was admitted to the Jewish Hospital Oct. 11, 1940, with a history of weakness and increasing fatigue for the preceding seven years, dyspnea for five years, swelling of the abdomen and lower extremities for two years, and cough for four days.

Her family history was noncontributory. There was no history of rheumatic fever, tonsillitis, or other infectious diseases.

Eight and a half years previously she had several attacks of pain in the epigastrium and right upper quadrant of the abdomen, radiating to the back, and associated with nausea and vomiting. One year later, during her pregnancy, she had another attack which was diagnosed as gall bladder disease. No cardiac or hepatic disorder was noted at this time.

(We are indebted to the Beth Israel Hospital, of New York, for the following history and data, most of which were obtained after the patient's death.)

From the Jewish Hospital of Brooklyn, Medical Service of Meyer A. Rabinowitz, M.D.

Received for publication April 4, 1941.

On Jan. 14, 1936, she was admitted to the Beth Israel Hospital with the complaint of fatigue of two and one-half years' duration. This occurred after her last pregnancy (1933), when she noted increasing fatigue—she was "run down" and "washed out." Her ability to do her everyday work had definitely decreased. She had never been disturbed by climbing two flights of stairs, but now found herself quite exhausted, very short of breath, and disturbed by the rapid beating of her heart. She could not stand for any length of time without support. The fatigue and breathlessness increased. Two months before admission she had generalized itching; this lessened considerably just before entering the hospital. Her physician, whom she consulted three weeks prior to admission, said she had some form of "heart trouble." He did not notice any hepatic enlargement. There was never any jaundice. She had lost 10 pounds in the two years prior to her admission. She also was possibly in her climacteric period, for her menstruation was irregular and she had vasomotor phenomena.

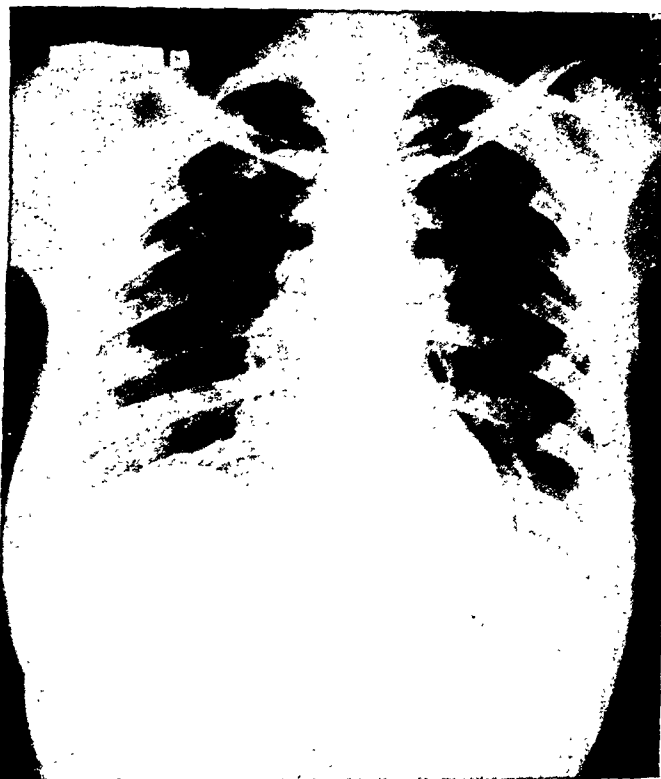


Fig. 1.—Teleroentgenogram of chest taken Jan. 16, 1936. The heart is normal in size and shape. The lungs are clear.

Examination at that time showed a normal pulse rate, temperature, and respiratory rate. She did not appear acutely ill and she showed no dyspnea. The sclerae were slightly icteric. There was a peculiar flushing which varied greatly with emotional changes. This, the patient stated, she had had for as long as she could remember. There were numerous excoriations over the entire skin surface, especially the trunk. There was no engorgement of the veins of the neck. The lungs were normal. The cardiac apex impulse was barely palpable 8.5 cm. from the midsternal line. Normal sinus rhythm was present. At the apex there was a systolic murmur. In the pulmonic area there was a harsh systolic murmur which occupied most of systole. These murmurs were recorded phonocardiographically. The pulmonic systolic murmur was said to be audible in the left interscapular area, but this was not confirmed phonocardiographically. The pulses were regular and of good quality. The blood pressure was 102/78. Examination of the abdomen revealed no ascites or collateral circula-

tion on the anterior surface; there were, however, some dilated veins over the lower part of the back. The liver was enlarged, extending to the umbilicus. The mid-portion of the anterior surface was extremely convex and felt somewhat cystic. The spleen was not felt. There was no edema of the lower extremities, and there was no clubbing of the fingers or toes.

Roentgenograms of the chest, taken Jan. 17, 1936, showed that the lungs were normal. The heart was normal in size, shape, and position. The roentgenokymogram was normal. The aorta appeared elongated. Oblique views showed no auricular or ventricular enlargement. Roentgenograms of the abdomen showed the large mass in the right upper quadrant. The gall bladder was displaced, but its function was normal. Excretion pyelograms showed nothing except a displaced right kidney. The electrocardiogram was normal, except for low voltage; the rate was 79, and left axis deviation was present. The urine was negative. The erythrocyte count was 4,000,000, with a hemoglobin of 65 to 75 per cent. The venous pressure was 6 cm. The icteric index was increased. The cholesterol was 263 mg. per 100 c.c. of serum. The arterial blood carbon dioxide content was 43.0 per cent. The oxygen saturation was 92.4 per cent. The venous blood carbon dioxide content was 48.7 per cent, and the oxygen saturation, 67.4 per cent.

On her fourteenth day in the hospital the patient developed fever and became markedly jaundiced. Her liver increased in size. Operation was advised, but she refused, and was discharged Feb. 6, 1936, with a diagnosis of hepatomegaly of unknown origin.

She was readmitted for operation Feb. 23, 1936. A diagnosis of cyst of the liver was made. On Feb. 24, 1936, drainage of numerous cystic cavities was performed. The bloody tissue that was obtained gave the appearance of liquefaction necrosis of liver tissue. On the posterior surface of the liver, just below the point at which the liver becomes extraperitoneal, corresponding to the junction of the hepatic vein and vena cava, there was a firm mass about the size of a half dollar and approximately 1 cm. in thickness. It looked like a malignant tumor, but it could not be excised because of its position. The pathologic report was "bloody fluid with necrotic material." She was discharged April 11, 1936.

(We are indebted to the Beth David Hospital for the following data.) She entered the Beth David Hospital Oct. 25, 1937, with a purulent discharge from a sinus at the site of the operation. She was again operated on, and a huge abscess cavity was found and drained. The pathologist reported suppurating granulating tissue. Lipiodol and thorotrast studies confirmed the presence of the cavity. She was given emetine therapy while in the hospital, and was discharged in an improved condition Dec. 5, 1937.

The patient was confined to her bed thereafter. There was a gradual onset of edema of the lower part of the body and extremities, which became markedly indurated. For eight months she received digitalis and 2 c.c. of mercupurin intravenously every three or four days, and then intramuscularly. A few days before admission she "caught cold," and, because of a cough and increasing dyspnea, she was admitted to this hospital. She had lost 25 pounds in the five months preceding her admission.

On admission the temperature was 100.2° F.; the pulse rate, 100; the respiratory rate, 32; and the blood pressure, 78/60. She was poorly nourished and appeared chronically ill. She had a peculiar, reddish-purple cyanosis—a violaceous color—most marked over the malar areas, with a butterfly configuration, and a mottled formation over the rest of the body. She seemed to be pigmented, but pressure obliterated all color, which readily returned.

She spoke with a weak, but husky, voice. The vocal cords showed hyperemia. The neck veins were markedly engorged and prominent. There was no tracheal tug.

The fundi were normal. The lungs were resonant throughout. There were fine râles at the base of the right lung. Medium moist râles and rhonchi were heard over the whole of the chest posteriorly, and in the axillae. The veins over the anterior chest wall were dilated.

Percussion showed that the heart extended to the left anterior axillary line. The apex beat was not felt. Inconstant, rough, systolic and diastolic murmurs were heard at the apex. A roughened systolic and a short blowing diastolic murmur were heard at the aortic area. The right brachial and radial pulsations were absent; the left brachial pulse was strong.

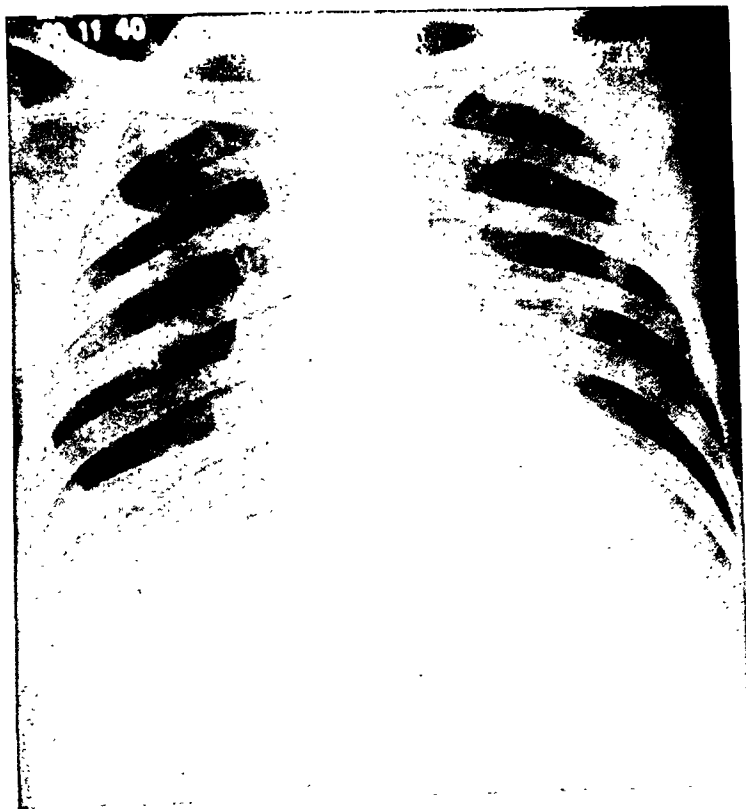


Fig. 2.—Teleroentgenogram of chest taken Oct. 11, 1940. There is slight cardiac enlargement. The lungs are not remarkable.

There was marked edema of the abdominal wall. A well-healed, large scar was present in the right upper quadrant. The liver was two fingerbreadths below the costal margin. It did not pulsate. Pressure on the liver did not increase the size of the veins of the neck. There was marked edema over the sacrum.

The lower extremities showed mottled cyanosis and extreme edema. The arms and forearms were tense from edema. The extremities were of normal temperature.

Fluoroscopic and radiographic examination of the heart was rather difficult because of the patient's precarious condition. Under the fluoroscope it was noted that the amplitude of the pulsations of the left and right ventricles was not appreciably impaired, and no gross auricular enlargement could be demonstrated. There was no evidence of calcification of the pericardium. There was a small amount of fluid in the right costophrenic sinus; the lung fields otherwise were clear. Her condition did not permit radiopaque visualization of the cardiac chambers by the Robb-Steinberg technique.

The electrocardiogram on Oct. 11, 1940, showed a ventricular rate of 100, normal sinus rhythm, and a P-R interval of 0.16 second. The main deflection and the T wave

were isoelectric in Lead I. Lead IVF was normal. The entire tracing showed extremely low voltage. The electrocardiographic diagnosis was severe myocardial involvement. Another tracing, made on Oct. 23, 1940, showed no change.

Laboratory Data.—The blood Kline reaction was negative. No methemoglobin or sulfhemoglobin was demonstrated spectroscopically. Blood: urea nitrogen, 26.4 mg. per 100 c.c. serum; icteric index, 10.6; phosphorus, 2.6 mg.; phosphatase, 14.2 units; chlorides, 388 mg.; sodium, 312 mg.; potassium, 18.1 mg.; cholesterol, 78.4 mg.; free cholesterol, 42.0 mg.; free cholesterol, 50 per cent; total protein, 4.65 Gm.; albumin, 1.96 Gm.; globulin, 2.69 Gm.; serum A./G. ratio, 0.73. The prothrombin time was 14.4 seconds. Urine: specific gravity, 1.022 to 1.018; one-plus albumin and an occasional leucocyte. The sedimentation time was 70 mm. per hour. The hemoglobin was 56 to 67 per cent; the erythrocyte count, 2,700,000; and the leucocyte count, 7,000 to 9,800. *Circulation Studies*, Oct. 28, 1940: Venous pressure (jugular vein), 20.4 cm. of water; saccharine time, neck-to-tongue, sixteen seconds; ether time, neck-to-lung, seven and one-half seconds.

Except for one day of fever, just before death, the patient ran an afebrile course. She was drowsy most of the time. The administration of oxygen produced no apparent improvement. She became weaker and more stuporous and died after three and one-half weeks in the hospital.

Discussion.—There was great difficulty in arriving at a satisfactory diagnosis. It was apparent that the patient was suffering from a tricuspid type of congestion; i.e., the inflow type of Vollhard, the hypodiastolic type of Fishberg, or, as Pollitzer described it, a paracardial adiasstolic congestion.

Because of the intense cyanosis, consideration was given to pulmonary artery sclerosis and endarteritis proliferans and pulmonie stenosis. Functional incompetence of the tricuspid valve is usually associated with lesions of the left side of the heart or conditions marked by increased tension in the pulmonary circuit. There were no indications that any of these factors were present. Organic tricuspid stenosis is usually associated with mitral stenosis. There was no evidence of the latter, and the right auricle was not enlarged. There was some evidence to support the clinical concept of constrictive mediastinopericarditis. However, there was no calcification of the pericardium and there was no reduction in the amplitude of the pulsations of the right and left ventricles. Chronic, fibrous, parietal myoendocarditis could produce the same picture. Consideration was also given to primary tumor of the auricle and secondary neoplastic disease, with involvement of the superior and inferior cava and right auricle.

Autopsy.—The following are the important pathologic changes:

The pericardial cavity contained approximately 60 c.c. of a clear, amber fluid. The pericardium was smooth and glistening and in no place constricting. The superior and inferior venae cavae were patent throughout. The heart measured 10 cm. across the base and 9.8 cm. from apex to base. It weighed 220 Gm. The apex was pointed and made up of the left ventricle. The epicardium was smooth and glistening. The right atrium was distended with post-mortem blood clot. Its endocardium was pearly gray; this involved the entire wall and spread between the muscle bundles

of the auricle. There was a firm, raised, gray plaque just proximal to the right atrioventricular orifice. The right atrioventricular orifice was shaped like a fish mouth, and barely admitted the tip of the little finger. The valve leaflets were fused, and the free margins were greatly thickened. They were pearly gray, firm, and inelastic. The right atrioventricular orifice measured 4.5 cm. in circumference. The chordae tendineae were fused, shortened, and thickened. The right ventricular wall measured less than 0.7 cm. in thickness. The papillary muscles were small and



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 1 2 3 4 5 6 7 8 9 10 11 12
 centimeters

Fig. 3.—Photograph showing stenosis of the pulmonary valves. There is hypertrophy of the right ventricular myocardium.

flattened. The pulmonary orifice was similarly stenosed, and admitted little more than the tip of the probe. When spread out, it measured 3 cm. in circumference. The valve leaflets which were distinguishable were pearly gray, rigid, and fused. There was no evidence of patency of the ductus arteriosus or the foramen ovale. The left atrium was dilated, and the musculature was flattened. The endocardium was opaque, soft, and gray. The left atrioventricular orifice measured 9 cm. in circumference; its leaflets and chordae tendineae were delicate. The wall of the left ventricle measured 1.5 cm. in thickness. The aortic orifice measured 7.5 cm. in circumference; the valves were delicate and fenestrated.

Microscopic section showed fibrosis of the tricuspid and pulmonary valves and of the endocardium of the right auricle. There were splitting and reduplication of the elastic layer, with the formation of dense, fibrous, collagenous connective tissue.

Evidence of a previous inflammatory lesion was seen at the rings of the tricuspid and pulmonary valves, as manifested by new blood vessels and occasional round-cell infiltration.

The ileum presented numerous nodular masses, rather firm in consistency, and yellow brown in color. These on section revealed the typical appearance of argentaffine cell neoplasm. Metastases to the regional mesenteric lymph nodes and several to the liver were found. The metastasis in the liver was broken down, pseudocystic, and contained hemorrhagic and tumor tissue.



Fig. 4.—Photograph showing stenosis of the tricuspid valve with fibrous endocarditis of the right auricle.

COMMENT

The diagnosis of tricuspid and pulmonic stenosis was not made because of the unusual clinical and roentgenologic phenomena. The marked fibrous endocarditis of the right atrium prevented the dilatation and hypertrophy of that chamber which is commonly associated with tricuspid stenosis. In pulmonic stenosis, besides the valvular defect, right ventricular hypertrophy and dilatation are usually found. It is quite probable that the marked tricuspid stenosis impeded the blood flow to the right ventricle to such an extent that the work of the ventricle was decreased.

Carcinoids of the intestine are polypoid growths which contain groups of epithelioid cells, cuboidal or cylindrical, granular and argentaffine, arranged in small groups or in broader bands. The uniform size, regular position, opacity, and lack of hyperchromatism indicate only moderate malignancy. Metastasis, which is uncommon, takes place in the mesenteric lymph nodes and liver.

CONCLUSION

A case of tricuspid stenosis and pulmonary stenosis, with fibrous endocarditis of the right auricle, is reported. This combination without other valvular defects is exceedingly rare, and the association with right auricular mural endocarditis is unique. The cause of the inflammatory process was not ascertained.

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RIGHT-SIDED HEART FAILURE (COR PULMONALE) CAUSED BY CHEST DEFORMITY

CASE REPORT

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DEFORMITY of the thorax as a cause of right ventricular failure is rare. Most of the reported cases are in the older French and German literature. Corvisart,¹ as early as 1806, performed an autopsy on a hunchback who died with symptoms of cardiac failure and found dilatation of the right auricle and ventricle. He attributed this to the increased resistance offered by the distorted blood vessels in the chest. Finley,² in 1921, remarked on the "almost complete absence" in English medical literature of any reference to the effects of scoliosis on the thoracic viscera. He reported 4 cases of extreme deformity of the thorax, resulting in hypertrophy and dilatation of the heart, with cardiac insufficiency. The left ventricular hypertrophy which he found in addition to the right ventricular hypertrophy in two of these cases was attributed to constriction of the aorta from the sharp curves resulting from the deformed vertebrae. Bachmann,³ in 1899, reported a detailed study of 197 patients with severe scoliosis and kyphosis that came to autopsy. He noticed that displacement of the heart upward and in the opposite direction to the scoliosis was a very frequent occurrence. Death was caused by heart failure in 116 (59.4 per cent) of these cases, but in 72 it was secondary to pulmonary disease rather than to the chest deformity alone. A number of isolated reports have been published. For a review of these cases, one is referred to the papers by Boas⁴ and Edeiken.⁵ Reid,⁶ in 1930, reported the case of a 16-year-old girl who died of cardiac hypertrophy and dilatation caused by a chest deformity of fourteen years' duration. Chapman, Dill, and Graybiel,⁷ in 1939, in a complete review of the subject, were able to collect from the literature 126 cases of fatal heart failure caused by chest deformity. They added 4 cases of their own. Clawson⁸ found, in the records of the Department of Pathology of the University of Minnesota from 1910 to 1938, inclusive, 69 cases of primarily right-sided failure among 4,678 cardiac deaths. Four of these 69 cases were instances of chest deformity. Hallock and Rigler,⁹ in 1941, in a clinical series of 38 cases of cor pulmonale, found one in which there was a thoracic deformity. This was in a 17-year-old hunchback.

The following case is reported because of its rarity and the necessity of recognizing deformity of the chest as an etiologic agent in certain cases of heart failure.

From the Luther Hospital, Eau Claire.

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CASE REPORT

A 27-year-old woman was admitted to Luther Hospital in an orthopneic, markedly cyanosed condition. She had had increasing dyspnea on exertion for several months, and occasional attacks of palpitation in the preceding three or four years. One month before admission she suddenly became more cyanotic, dyspneic, and fatigued. The patient had poliomyelitis at the age of four years, but recovered completely, with no residual paralysis. At the age of nine years she severely injured her shoulder and neck in a fall from a grandstand. This was followed by gradual elevation of her right shoulder, with the later development of marked kyphoscoliosis. An orthopedic consultant at the time regarded the deformity as traumatic in origin. She remained a semi-invalid.



Fig. 1.—Roentgenogram of chest taken post mortem, showing severe chest deformity.

Physical examination revealed a small woman who weighed approximately 90 pounds. Her temperature was 99.2° F., and her pulse rate was 124. Her blood pressure was 98/65. The thorax was markedly deformed by scoliosis, and there was an anteroposterior convexity. She was cyanotic, markedly dyspneic, and in a critical condition. There was no edema or ascites. Examination of the heart revealed distant sounds with an increased rate. No murmurs were heard. A few moist râles were present at the bases of both lungs. The liver was enlarged; it extended several centimeters below the costal margin. The remainder of the examination did not reveal any important abnormalities. Urinalysis was negative except for one-plus albumin. No other laboratory work was done.

The clinical diagnosis was acute heart failure, and routine treatment was initiated. However, she did not respond; the dyspnea and cyanosis increased, and she died the day after admission.

Autopsy.—The body was 150 cm. in length, and its weight was estimated at 90 pounds. The chest was markedly deformed. There was marked cyanosis of the entire face and neck. Edema was absent. Examination of the abdominal cavity revealed approximately 100 c.c. of straw-colored fluid and downward displacement of the liver. It extended 11 cm. below the right costal margin. The pleural cavities contained no fluid or adhesions. There was marked deviation of the midthoracic spine to the right, associated with lateral rotation and kyphosis. There was also a lateral rotation to the left of the lumbar vertebrae, with anterior displacement of the lower thoracic vertebrae. The ribs of both sides, particularly on the right, showed considerable displacement. The pericardial sac had a transverse diameter of 11 cm.; it contained no excess fluid.



Fig. 2.—Marked hypertrophy and dilatation of the right ventricle.

The heart weighed 200 Gm. The epicardial surfaces appeared normal. There was marked hypertrophy of the right side of the heart. The right ventricle and right auricle were considerably larger than the left. The right ventricular wall was markedly hypertrophied; it measured 1.3 cm. in thickness. There was also considerable dilatation of the right ventricle (Fig. 2). The left ventricle appeared to be of normal size. The appendages, endocardium, and valves showed no abnormalities. The septum was reddish brown in color and showed no streakings. The root of the aorta appeared normal. The coronary arteries were patent and showed a minimum of sclerosis.

The right lung weighed 200 Gm., and the left, 300 Gm. Both lungs were displaced anteriorly. The lungs were grayish pink in color and showed a minimum of anthracosis. There was no apical scarring. The consistency of the left lung was

greatly increased. There was no evidence of emphysema. On section, both lungs were dark red and showed considerable generalized edema. There was no consolidation. The pulmonary arteries, including the trunk, were patent and showed no congenital anomalies. There was no atherosclerosis or dilatation. However, because of the peculiar position of the lungs and heart, there was some distortion of the main pulmonary artery. The aorta showed a minimum of sclerosis. It followed the tortuous course of the spine and showed no changes in circumference.

The liver weighed 800 Gm. It was yellowish brown, and its consistency was normal. On section, it showed the mottled nutmeg appearance of passive congestion. The spleen weighed 50 Gm., and the kidneys, 150 Gm. each. They appeared normal except for evidence of passive congestion. The pelvic organs appeared normal. No enlarged lymph nodes were found. The brain and spinal cord were not removed.

Microscopic Examination.—Sections of the liver showed severe chronic passive congestion. The lungs showed edema, with mild emphysema. There was no evidence of any pulmonary arteriosclerosis. The remaining organs appeared normal.

DISCUSSION

The mechanism by which the right-sided cardiac hypertrophy and failure are brought about in chest deformities is not difficult to understand. The deformed thorax is small and the diaphragm is high. Since the thoracic deformity is usually established in childhood, the chest does not develop in proportion to the rest of the body. In cases of severe kyphoscoliosis, marked distortion and displacement of the larger pulmonary vessels exists. As a result, the volume of the lungs and the vital capacity are greatly reduced. Emphysema is frequently a compensatory phenomenon. The pulmonary artery may become dilated. The pressure within the pulmonary circulation becomes elevated. A greater burden is placed on the right side of the heart. This eventually leads to right ventricular hypertrophy, which may be followed by dilatation and cardiac insufficiency. Cardiac failure is usually a gradual process, extending over a long period of time. Boas⁴ calls attention to the difficulty of interpreting physical signs in these cases because of the great deformity of the chest. It is often impossible to ascertain whether or not cardiac hypertrophy is present, and murmurs are difficult to recognize. Electrocardiograms usually reveal right ventricular hypertrophy. Roentgenologic studies show enlargement or dilatation of the pulmonary artery and conus, without evidence of any significant hypertrophy of the left ventricle. Once the signs of myocardial insufficiency appear, as in other cases of cor pulmonale, the prognosis is extremely poor, for these patients do not respond well to digitalization. Chapman, and associates,⁷ found that the average age at death of 79 such patients was 30 years. The only hope lies in early treatment of spinal deformities.

SUMMARY

The case of a 27-year-old woman who suffered from severe kyphoscoliosis since childhood is reported. Death was caused by right-sided cardiac hypertrophy and insufficiency secondary to the chest deformity. Attention is called to the part severe chest deformities may play in the development of right ventricular hypertrophy and failure.

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JUVENILE ELONGATION OF THE AORTA

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CASE REPORT

H. C. C., a Chinese, aged 12 years, was seen in the United Hospital in January, 1940. He gave a history of dislocation of the right wrist as a result of a fall from a height of about 12 feet, three years earlier. Discharging sinuses had been present for about two years. The clinical impression was traumatic dislocation of the right wrist, with chronic osteomyelitis. Routine fluoroscopic examination of the chest revealed normal lungs and diaphragm. The unusual changes that caught the eye were a markedly elongated and tortuous aorta, with its upper end extending well into the left upper lung field, and prominence of both ventricles, especially the left. Pulsations appeared normal. The retrocardiac space was clear. A roentgeno-



Fig. 1.

gram taken with a target-film distance of 250 cm. (Fig. 1) confirmed the fluoroscopic observations. The heart appeared slightly wider and larger than normal. The general outline of the heart was somewhat sabot-shaped, with moderate rounding of the left border and less of the right. The aorta appeared moderately elongated, and had a rather tortuous knob, the superior border of which corresponded

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in level to the fourth thoracic vertebra. The cardiothoracic ratio was 0.54, and the width of the aortic shadow was 5.4 cm. The ribs showed no abnormality.

Because of the striking roentgenologic abnormality, attention was paid to other systems, particularly the cardiovascular. The patient, however, gave no history of cardiovascular disease. There was no cyanosis, edema, or clubbed fingers. The blood pressure was 110/60. The urine and stool were normal. The hemoglobin was 85 per cent, and the leucocyte count, 9,800. The differential count was normal. There were no stigmata of congenital syphilis. Unfortunately no electrocardiogram was available at that time. Dr. C. Wu made a detailed examination of the cardiovascular system. Auscultation revealed hyperdynamic heart sounds, with a Grade I systolic murmur at the aortic area; the first sound at the apex seemed to be reduplicated (? normal third sound). There was nothing else remarkable.

In the absence of any other clinical or laboratory abnormalities, it was difficult to account for the roentgenographic appearance of the aorta and heart. It was therefore felt that several possibilities should be considered, among which were (1) a congenital anomaly, (2) juvenile arteriosclerosis (clinically latent, perhaps as a result of toxic absorption from the chronic osteomyelitis of the right wrist), and (3) juvenile hypertension.

DISCUSSION

A search through the recent literature showed no similar case. No comparative information could be gleaned from roentgenologic sources. There was but scant mention of the normal aorta and its variations in childhood in roentgenologic texts, including Roesler's,¹ Polevski's,² and Vaquez and Bordet's,³ or in textbooks of cardiology, such as White's.⁴ Pathologic or congenital enlargement or elongation was not described. Some textbooks of medicine and cardiology briefly mentioned the occurrence of arteriosclerosis or of hypertension in childhood, but said nothing about any roentgenologic changes. Occasional reports of juvenile arteriosclerosis have appeared in the literature. Guild, Kindell, and Gibson⁵ described two such cases in detail, in one of which there was mild involvement of the aorta, but no roentgenograms were shown. The writer therefore feels that the roentgenographic changes in the case reported here are unique, in spite of uncertainty concerning the causative factor. It appears that thorough studies of the roentgenologic appearance of the normal aorta and its variations in childhood, not excluding pathologic changes, are indicated.

SUMMARY

Marked elongation and tortuosity of the aorta, with some hypertrophy of both ventricles of the heart, particularly the left (but with no frank clinical evidence of disease of the cardiovascular or renal system), were discovered roentgenologically in the case of a boy, 12 years old, who was suffering from traumatic dislocation of the right wrist complicated by chronic osteomyelitis. It was felt that the unusual appearance of the aorta and heart might be explained by (1) a congenital abnormality, or (2) some juvenile degenerative or hypertrophic change

brought about by unknown factors (toxic?) which were perhaps related to the chronic infection of the right wrist.

The writer is indebted to Dr. S. H. Wang for his invaluable help in the preparation of this article.

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TWO CASES OF DISSECTING ANEURYSM OF THE AORTA, WITH ANTE-MORTEM DIAGNOSIS

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IN 1933, Shennan collected from the literature three hundred seventeen cases of dissecting aneurysm of the aorta, in six of which the diagnosis had been made antemortem. Since that time there have been numerous reports, indicating an increasing interest in, and more frequent recognition of, this morbid state. One hundred fifty-one cases have been reported in the American literature since Shennan's review. Of these, an ante-mortem diagnosis was made in thirty-four. To this group we are adding two cases in which the diagnosis was made clinically.

Two hundred eighty-three cases of hypertension of various kinds have been seen in the Lilly Laboratory for Clinical Research at the Indianapolis City Hospital during the past four years. Two patients in this series developed dissecting aneurysm of the aorta, which is an incidence of less than one per cent.

Of the one hundred fifty-one cases in the literature, hypertension was known to be present in one hundred seven. Of forty-two patients who had had no previous blood pressure recordings, twenty-three were found to have hypertension, and the other nineteen were in a state of shock. Two patients had a normal arterial pressure before and after the onset of symptoms. Since dissecting aneurysm is occasionally a complication of hypertension, and is associated with it in the majority of cases, we are presenting the features which characterize this condition. Coronary disease, with subsequent occlusion, is frequently observed in hypertensives. Yet these two conditions, although they present similar symptoms, have a different prognosis, i.e., some patients with coronary occlusion recover.

CASE REPORTS

M. S., a white man, aged 49, a manufacturer, complained of nervousness, headaches, nausea, blurred vision, and substernal pain. Ten years prior to admission to the Lilly Clinic it was found that his arterial pressure was slightly elevated. In May, 1939, he had a sudden, severe pain in the lower lumbar region which, he said, felt "as if someone hit me with a baseball bat." The pain radiated to the groin and inner aspects of the thighs. At that time he was in another hospital for two weeks. No abnormalities were noted, and the pain did not recur. In December, 1939, the patient had a cerebral hemorrhage which resulted in a disturbance of speech and mild facial paralysis. From that time he complained of headaches, nervousness, and palpitation. Three months later his physician made a diagnosis of malignant

From Lilly Laboratory for Clinical Research, Indianapolis City Hospital.
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hypertension because of papilledema, retinal hemorrhages and exudates, and a marked elevation of blood pressure. At three o'clock on the morning of admission the patient had a severe substernal pain which required a grain of morphine for relief. In the opinion of the referring physician, the patient had coronary occlusion.

Physical examination showed papilledema and moderate constriction and sclerosis of the retinal arterioles, with hemorrhages and exudates. The tongue deviated to the left and the mouth was drawn to the right. There was moderate cardiac enlargement, with a loud systolic murmur at the apex; intermittent gallop rhythm was present. The blood pressure was as follows: left arm, 222/158; right arm, 218/152;

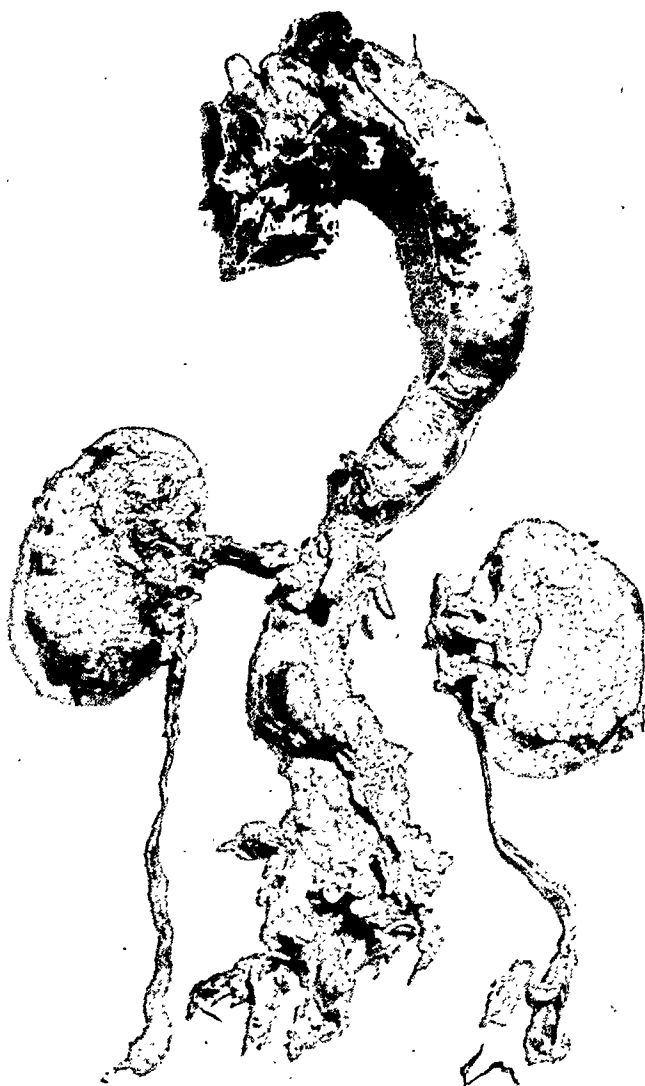


Fig. 1.—M. S., autopsy specimens, showing aorta, renal vessels, kidneys, and ureters.

left leg, 268/194; and right leg, 292/214. All of the reflexes were hyperactive. During the patient's hospital stay of twenty-eight days, the erythrocyte count fell from 4.9 to 4.0 million, and the hemoglobin from 100 per cent to 65.4 per cent. A leucocytosis of 14,000 persisted. The urea clearance averaged 35 per cent of normal, and the blood urea nitrogen ranged from 13.9 mg. per cent to 18.5 mg. per cent. Hematuria was present constantly. The transverse cardiac diameter was +27 per cent (Ungerleider-Clarke). A roentgenogram of the chest showed

some widening of the aorta. The electrocardiogram showed inversion of the T wave in all leads, and a biphasic QRS in Leads II and IV. The impression from the electrocardiogram was that coronary occlusion might have occurred. There was gradual improvement, as indicated by later electrocardiographic changes.

Because of the constant substernal and epigastric pain, without fall in blood pressure, a diagnosis of malignant hypertension and dissecting aneurysm of the aorta was made. In order to confirm the diagnosis, a fluoroscopic examination of the chest was done, and this revealed generalized widening of the aorta. The aorta cast an unusually dense shadow.

During his hospital stay the patient complained almost constantly of pain in the back of the neck, behind the sternum, and in the epigastrium. On the twentieth day a to-and-fro friction rub was heard along the left border of the sternum. The pain increased in severity and his pulse became irregular. There was a moderate febrile reaction and the leucocytosis persisted, but no changes were recorded in the electrocardiogram. Three days later the pain became almost unbearable and continued unabated. There were marked abdominal distention and occasional projectile vomiting. Persistent gallop rhythm developed, and the heart sounds were sharp and snapping. The patient died unexpectedly, while asleep, on the twenty-eighth day after the onset of pain.

Post-mortem examination by Dr. H. C. Thornton showed that the left pleural sac contained about 1000 c.c. of serous fluid. The lung was collapsed and the mediastinum was pushed to the left by a large blood clot in the mediastinum. The clot weighed 2128 Gm. The heart weighed 528 Gm., and the myocardium was pale and flabby. There were moderate atherosclerosis of the aorta and marked sclerosis of the coronary arteries. No occlusion of the coronary vessels was noted.

There was a ragged opening in the aorta, 2.5 cm. in diameter, on the superior and lateral aspect, about 2 cm. distal to the left subclavian artery. A dissecting aneurysm involved the distal portion of the arch, all of the thoracic portion of the aorta, and the upper portion of the abdominal aorta as far as the superior mesenteric artery, down which it extended a short distance. In the thoracic aorta the aneurysm measured 2 cm. in thickness and extended 3 cm. around the wall. The lumen was compressed by the aneurysm, which was filled with a fresh thrombus. Another partially healed dissecting aneurysm involved the lower abdominal aorta and the left common iliac artery. An opening 5 mm. in diameter, with smooth edges, was found on the anterior wall of the aorta about 3 cm. proximal to the bifurcation. This opening led into the aneurysm, which extended upward from the opening about 5 cm., and downward to the bifurcation and along the left common iliac artery. In the lower aorta the aneurysm was 2.5 cm. in diameter, and the upper portion was occupied by an old, pale, firm, apparently organized thrombus. There was a third dissecting aneurysm in the left renal artery which partially occluded the lumen of the vessel.

E. F., a white man, aged 54, a salesman, was admitted to the Lilly Clinic Sept. 8, 1939, complaining of severe abdominal, interscapular, and precordial pain of ten days' duration. The patient had first noticed headaches, nocturia, and vertigo five years before, at which time his blood pressure was 200/120. Two years later, roentgenologic examination revealed enlargement of the heart, with widening of the aortic arch and tortuosity of the descending aorta. The electrocardiogram was normal. The vertigo, nocturia, and headaches persisted, but no physical abnormalities were noted except the elevation in blood pressure. Symptomatic improvement occurred on thiocyanate therapy. Two months before admission he had severe interscapular and abdominal pain which lasted one-half hour. A month later he had a severe, stabbing pain in the right, anterior part of the chest.

The present illness had begun suddenly while the patient was driving a car. He had a sharp pain between the scapulae, with abdominal cramps. When he tried to

stop the car he could not move his feet and legs. He pulled himself out of the car because he wanted to urinate and defecate, but was unable to do either. After lying by the roadside for an hour he managed to drive to a physician's office. The pain was temporarily relieved by one-half grain of morphine.

Physical examination on admission showed severe constriction and moderate sclerosis of the retinal arterioles. There was increased precordial activity, and a roughened, accentuated first sound was heard in the mitral area. The blood pressure was 244/144 in the left arm. Marked rigidity of the abdominal wall was present, and there was a Babinski reflex on both sides. The erythrocyte count was 3.86 million, and the leucocyte count gradually increased from 9,500 to 14,000. The blood urea nitrogen was 29 mg. per cent, and the urea clearance was 53.8 per cent of normal. The electrocardiogram showed left axis deviation.



Fig. 2.—E. F., Sept. 13, 1939. Roentgenogram showing widening and increased density of the aortic shadow.

Moderate doses of morphine failed to relieve the patient's pain, and, on the fifth day of his hospital stay, hiccough became a distressing symptom. In order to differentiate dissecting aneurysm of the aorta from diaphragmatic irritation of unknown origin, fluoroscopic examination was done. There was widening of the

aortic arch and the descending aorta. About 2 cm. above the diaphragm there was a marked out-pouching of the aortic wall to the left. Later on the same day the patient died suddenly while talking with the resident physician. The clinical diagnosis was essential hypertension and rupture of a dissecting aneurysm of the aorta.

At post-mortem examination the left thoracic cavity was completely filled with freshly clotted blood. The left lung was partially collapsed. The transverse diameter of the pericardium measured 15 cm. The ascending aorta was relatively normal. Between the intima and muscularis of the descending aorta there was an organized thrombus which measured 2 cm. in thickness and 11 cm. in length. The thrombus completely encircled the aorta and extended downward to about 2 cm. above the diaphragm, i.e., to the point of rupture on the lateral aspect of the vessel. The muscularis was friable and necrotic. The intima was covered with many atheromatous plaques, and, at two points in the first part of the descending aorta, there were necrotic areas. In the center of one of these there was a communication between the lumen of the vessel and the aneurysmal sac. The dissection continued along the arch of the aorta to within a few centimeters of the aortic valve. The heart weighed 480 grams; the hypertrophy was, for the most part, of the left ventricle. The coronary arteries were moderately sclerosed. Another dissecting aneurysm was found in the pancreatic artery at the point of its entrance into the gland.

The important microscopic abnormality in the aorta was thickening of the adventitia with many fibroblasts. The adventitia had a loose, edematous appearance, and contained numerous polymorphonuclear leucocytes and lymphocytes. The majority of the vasa vasorum were thrombosed. There was a large thrombus in the media, the inner portion of which showed marked degeneration and necrosis.

DISCUSSION

We wish to stress the points in a typical case of dissecting aneurysm which we feel are important in making a diagnosis.

If a patient is known to have high blood pressure it is important that frequent readings be recorded. It is a rule in this clinic that the arterial pressure of each patient must be taken in each extremity during the course of his physical examination at the time of admission. If there is any abnormality in the readings, they are repeated frequently. Otherwise, measurement twice daily in the left arm is the rule. A persistently high blood pressure with the symptoms of coronary occlusion should cause one to question the latter diagnosis.

A continued, agonizing pain, radiating from the area of dissection of the aorta, is the most outstanding symptom. The examining physician may discredit the patient's complaints because of the improbability that comparatively good health could be followed so quickly by desperate illness. Pain, with temporary paralysis of the extremities, is usually caused by actual dissection of the main artery, thrombosis of a vein, or embolism. The pain of coronary occlusion seldom radiates below the sacrum, but in dissecting aneurysm it commonly radiates to the legs. Associated with the pain, coldness and diminution or absence of the pulsations of the arteries are observed. The latter may be transient.

There is a peculiar grayish cyanosis which accompanies the patient's appearance of anxiety. It is not the pallor of shock or the cyanosis of respiratory distress, and it is not relieved by the administration of oxygen.

The temperature may be subnormal if the patient is in shock, or moderately elevated. There is usually an increase in the leucocyte count. Of the one hundred fifty-one cases reviewed, in forty-five there was a leucocytosis of 9,500 to 34,000; in one hundred three no count was recorded; and, in three, the count was normal. The importance of the progressive anemia which follows extensive bleeding into the aortic wall has not previously been stressed. In one hundred thirty-one of the cases reviewed, no erythrocyte count was recorded; sixteen patients were known to have progressive anemia, and four had no anemia.

Taking a roentgenogram of the chest is a routine procedure in most clinics. Certainly any patient with hypertension should have a teleoroentgenogram. If the cardiac, aortic, or mediastinal shadow is abnormal, subsequent roentgenograms may disclose progressive enlargement. Fluoroscopic examination is usually an aid in the diagnosis of aneurysm. Thirty-one of the one hundred fifty-one patients had roentgenologic abnormalities suggestive of dissecting aortic aneurysm; one hundred fifteen had no roentgenologic examination; and only five had normal shadows.

What the electrocardiogram will show depends upon the degree of myocardial damage, the site of the dissection, and the state of the coronary arteries. Since this condition occurs most frequently in hypertensive patients, left axis deviation is common. If there is much coronary sclerosis there may be changes in the T waves and the S-T segment. Should the dissection involve the coronary ostia or the arteries themselves, there may be changes which are typical of myocardial infarction. The point is that there is no typical electrocardiographic pattern in this disease.

SUMMARY

In a series of two hundred eighty-three patients with hypertension, two developed dissecting aneurysm of the aorta. Although these two patients had signs and symptoms of coronary thrombosis, this diagnosis was ruled out by several significant features. In both cases the pain occurred first in the chest and then radiated to the shoulders, back, abdomen, or extremities. It was so agonizing that large doses of morphine failed to give relief. The blood pressure remained elevated, and, in the first case, it was not the same in the upper and lower extremities and was higher in the right leg than in the left. Mild fever, moderate leucocytosis, and anemia were present. Roentgenographic and fluoroscopic examination of the chest showed widening of the aorta and mediastinum. Post-mortem examination confirmed the diagnosis of dissecting aneurysm of the aorta in both cases.

We appreciate the assistance of Dr. Helen L. Crawford, of the Department of Roentgenology.

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Abstracts and Reviews

Selected Abstracts

Tocantins, L. M.: Loss of Prothrombin Activity in Plasma Exposed to Air Currents. *Proc. Soc. Exper. Biol. & Med.* 49: 251, 1942.

Exposure of citrated or oxalated plasma to an air current is followed by a rapid diminution in its prothrombin activity probably due to rapid evaporation and loss of CO_2 . Addition of CO_2 , even by saturating the plasma with expired air, restores prothrombin activity to its initial level, while bubbling oxygen through the plasma has no effect. Changes in CO_2 content of the blood may explain the difference in prothrombin activity of the blood entering and leaving the lungs. Asphyxia or hyperventilation may be expected to produce significant fluctuations in the prothrombin activity of the blood.

WILLIAMS.

Wakim, K. G.: Effect of Stimulation of Autonomic Nerves on Intrahepatic Circulation of Blood in Intact Animal. *Proc. Soc. Exper. Biol. & Med.* 49: 307, 1942.

The effect of stimulation of the sympathetic and parasympathetic nerves of anesthetized frogs and albino rats on the intrahepatic vessels was observed by transillumination of the intact liver. Stimulation of the nerve plexuses in the porta hepatis and around the hepatic artery of frogs by weak or strong tetanizing current caused constriction of the active sinusoids, some of which contracted to disappearance. Constriction appeared within two seconds after the beginning of stimulation and lasted for four to five seconds after discontinuance of stimulation. Immediately after pithing there was a marked reduction in the number of active sinusoids. This inactivity resulted in either a constrictor effect, leading to very narrow sinusoids containing hardly any corpuscles, or more commonly in stasis with the sinusoids packed full of corpuscles lying motionless in their lumina. After about fifteen minutes circulation began to recover in the inactive lobules, but more inactive sinusoids were seen than in an intact anesthetized frog. Stimulation of the plexus of nerves in the porta hepatis and around the hepatic artery in rats produced moderate blanching and constriction of the sinusoids. There was a latent period of about five seconds, and the sinusoids resumed activity about ten seconds after cessation of the stimulus. Arterial sinusoids were constricted more markedly than the venous ones. Arteriovenous anastomoses constricted to disappearance. Stimulation of both vagus nerves did not cause any perceptible changes in the circulation of the liver.

WILLIAMS.

Helmer, O. M., and Page, I. H.: Formation of Angiotonin-like Pressor Substance From Action of Crystalline Pepsin on Renin-Activator. *Proc. Soc. Exper. Biol. & Med.* 49: 389, 1942.

The observation by Croxatto and Croxatto that commercial pepsin at pH 2.0 reacts with renin-activator to form a pressor substance with properties similar to those of angiotonin was confirmed. Crystalline pepsin was found to react in the

same manner. The reaction between pepsin and renin-activator is halted at pH 6.5. The effect of pH on this reaction is quite different from the effect of pH on the formation of angiotonin from renin and renin-activator; angiotonin is formed abundantly at pH 6.5 to 7.0 but not at all at pH 2.0 to 4.0.

WILLIAMS.

Huidobro, F., and Braun-Menendez, E.: The Secretion of Renin by the Intact Kidney. *Am. J. Physiol.* 137: 47, 1942.

Profound lowering of the blood pressure by hemorrhage (4 per cent of body weight) or shock causes the liberation of renin by the intact kidney of normal anesthetized dogs. Renin can be detected in the systemic blood of these dogs. Renin could not be detected in the blood of nephrectomized dogs after hemorrhage or in normal dogs intoxicated with KCN or subjected to respiration of mixtures poor in oxygen. After short periods of 4 to 11 minutes of profound arterial hypotension renin could be detected in the systemic blood of normal dogs.

The inference is drawn that the kidney participates in the regulation of arterial blood pressure. When the blood pressure decreases the normal kidney secretes renin which through the formation of hypertensin tends to the restoration of normal blood pressure. Renin appears to be a substance which the body uses to maintain homeostasis.

AUTHORS.

Goss, C. M.: The Physiology of the Embryonic Mammalian Heart Before Circulation. *Am. J. Physiol.* 137: 146, 1942.

The following points concerning the fundamental or intrinsic powers of the myocardium have been made in the author's observation of early embryonic hearts: First, the power of spontaneous rhythmic contraction is possessed by each of the chambers and they have their own intrinsic rates. Second, the contraction of the myocardium progresses by a wave from one end of the chamber to the other. Third, the atrioventricular interval which makes coordination of the whole heart possible appears along with atrial contraction itself. Fourth, the spontaneous rhythm of the ventricle is inhibited by the atrium. Fifth, mechanical work, pumping the blood, begins after the preparatory development outlined above.

AUTHOR.

Cope, O., Brenizer, A. G., Jr., and Polderman, H.: Capillary Permeability and the Adrenal Cortex Studies of Cervical Lymph in the Adrenalectomized dog. *Am. J. Physiol.* 137: 69, 1942.

Lymph was collected from the cervical trunk of normal and adrenalectomized dogs under local anesthesia. The protein content of the lymph of the normal animals averaged 2.8 grams/100 c.c., and of the adrenalectomized 4.3 grams. The increase above normal was as great in the dogs in moderate as in severe insufficiency and was not merely an accompaniment of a moribund state. The finding offers direct evidence of an increase in capillary permeability in one region of the dog in adrenal insufficiency.

The significance of this protein increase in lymph to the osmotic equilibrium between blood plasma and extracellular fluid is discussed.

The flow of lymph was in general, but not consistently, reduced in insufficiency. The extracellular fluid volume, measured by means of thiocyanate, was increased as well as decreased.

AUTHORS.

Pappenheimer, J. R., and Maes, J. P.: A Quantitative Measure of the Vasomotor Tone in the Hindlimb Muscles of the Dog. *Am. J. Physiol.* 137: 187, 1942.

The hindlimb muscles of anesthetized dogs were perfused with defibrinated blood at constant pressure from a pump-lung circulation. The sciatic nerve to the muscles was left intact. At intervals the nerve was reversibly blocked by cooling and the changes of blood flow measured at different perfusion pressures. The blood perfusion could be interrupted by periods of Ringer perfusion.

With the blood vessels unconstricted (nerve blocked) the relations between the pressure and the flow of blood or of Ringer's solution were similar to those found by Whittaker and Winton (1933) in the isolated hindlimb.

During vasoconstriction the following changes occur in the pressure-flow curves: a. The pressure at which the pressure-flow curve of blood becomes approximately linear is increased. Below this pressure the slope diminishes and the curve approaches the origin. The extrapolated intercept of the linear part of the curve increases with increasing vasoconstriction. b. The Ringer pressure-flow curve is a straight line which intercepts the pressure axis at or near the origin. Its slope is diminished by vasoconstriction but its intercept is unaffected.

The apparent relative viscosity of the blood (ratio of Ringer flow to blood flow at constant pressure) is increased during vasoconstriction. The amount of increase varies in different muscles and in the same muscles with the degree of vasoconstriction and with the pressure. Extreme values for blood of normal corpuscular concentration are 2 to 8. At normal pressures the change of apparent viscosity accounts for about $\frac{1}{3}$ of the total change of resistance to blood flow caused by vasoconstriction.

For any constant degree of vasoconstriction the ratio of the Ringer flows at constant pressure in the unconstricted and in the constricted blood vessels is approximately equal to the ratio of the slopes of the pressure-flow curves of blood in the unconstricted and in the constricted vessels, both slopes being measured over the linear parts of their characteristics.

The evidence suggests that this ratio is independent of the viscosity and is a measure of the change in the average dimensions of the blood vessels. In the innervated preparation it is proposed as a measure of the vasomotor tone. Its value has varied from 1.0 (no vasomotor tone) to about 3.5. Reasons are given for supposing that the measure is quantitatively comparable in the muscles of different experiments.

AUTHORS.

Heilig, R.: The Pathological Heart Conditions in Hookworm Disease and Their Causes. *Indian M. Gaz.* 77: 257, 1942.

Sixty-five cases of uncomplicated severe hookworm anemia were selected among an unlimited material of ankylostomiasis, as it is found in Mysore, South India. The characteristic signs, which the heart presents in untreated cases, are bilateral dilatation, mitral configuration, a thumping first sound and a systolic murmur in the apical area, an accentuated pulmonary second sound and a harsh systolic murmur in the second left interspace different in character from that heard at the apex. On fluoroscopy an expansile pulsation of the heart contour is regularly seen; epigastric pulsation is frequently felt. The blood pressure is about 100-110 mm. Hg systolic and rarely more than 50-60 diastolic. The electrocardiogram always showed signs of a definite myocardial lesion such as a very low general voltage, depressed or downwards convex S-T junction and a flat or isoelectric T in all the leads. In fifty-nine (90 per cent) of these cases all the pathological signs elicited on percussion, auscultation, fluoroscopy and electrocardiography disappeared completely after four to six weeks of mere antianemic treatment with large doses of iron (Blaud's pills, gr. 90 per day) before deworming was per-

formed. In six cases, women all of them, the pathological heart condition deteriorated in all aspects in spite of perfectly satisfactory blood response to equally intensive antianemic treatment until the last hookworm was eliminated. Ten days to three weeks after complete deworming the same improvement of the heart condition was observed as it was seen in the other cases already before anthelmintic treatment was performed. These results point towards the existence of a hookworm toxin; the myocardial damage which is caused by its action could be overcompensated by improvement of the red blood picture in the majority of hookworm anemias, whereas a minority remained where its damaging influence continued independently of the blood condition, as long as more than three to five hookworms escaped destruction.

AUTHOR.

Moia, B., Inchauspe, L. H., Olmedo, R. C., and Battle, F. F.: The Electrocardiogram in Simultaneous Increase in Size of Both Ventricles. *Rev. argent. de cardiología*. 9: 1, 1942.

The effect on the electrocardiogram of simultaneous enlargement of both ventricles was studied in 96 young patients in which rheumatic aortic insufficiency coexisted with mitral stenosis. None of these patients received digitalis, nor had auricular fibrillation or signs of active carditis or pericarditis. The nonexistence of other factors, especially coronary disease, was thus presupposed.

From these 96 patients 20 were selected for this study because of the absence in their electrocardiograms of the characteristic alterations of aortic insufficiency or mitral stenosis. A case of arterial hypertension with pulmonary sclerosis was added in which necropsy showed the absence of coronary alterations of the stenotic type.

The electrocardiograms of these patients, apart from the absence of axis deviation, showed in the standard leads and in precordial leads CF_1 , CF_2 and CF_4 and in the sagittal derivations the following changes:

QRS.—Right axis deviation ($R_3 > R_2$) with absence of S_3 ; absence of definite axis deviation with S_3 ; triphasic complexes with positive initial deflection in L_4 or in L_3 and L_2 , with sometimes very deep S_3 .

ST segment.—Even in the absence of definite axis deviation the ST segment was depressed in only one (L_1) in two (L_2 and L_3) or in the three standard leads; depressed in L_1 and elevated in L_3 or elevated with a rectilinear stretch in L_3 .

T wave.—High voltage in one or more leads and negative, diphasic or flat in L_3 . The cases with alterations of the ST segment showed generally negativity or diphasism of T in L_1 , or diphasism in L_1 and L_2 with flat T_3 or negativity in the three leads especially in L_2 and with a conformation very similar to the so-called "coronary T wave."

Deep inspiration did not modify these patterns. Precordial leads did not show any definite alterations. In some cases the sagittal lead showed in L_3 a clear left type, the concordant ST deviation changing into the opposite.

The cause of these alterations and their diagnostic significance is discussed and attention is drawn to the fact that in many cases they are very similar to those alterations which appear in the electrocardiogram in cases of myocardial damage (ischemia, infectious diseases, etc.) and pericarditis.

AUTHORS.

Goldburgh, H. L., Baer, S., and Lieber, M. M.: Acute Bacterial Endocarditis of the Tricuspid Valve. *Am. J. M. Sc.* 204: 319, 1942.

In 26,007 necropsies there were 646 cases of acute bacterial endocarditis, an incidence of 2.5 per cent.

The mitral valve, singly, was most frequently involved (47.6 per cent) followed by the aortic valve, singly (25.4 per cent), mitral and aortic (18.7 per cent), and tricuspid, singly (3.1 per cent).

Lesions were limited to the tricuspid valve in 20 cases, an incidence of 3 per cent of acute bacterial endocarditis and 1 out of 1,300 autopsies.

Right-sided bacterial endocarditis occurred in 8.2 per cent of the cases.

Lesions involved the tricuspid valve alone in 9 of the 62 cases of pneumococcal bacterial endocarditis (14.5 per cent).

The lack of diagnostic auscultatory findings in acute bacterial endocarditis of the tricuspid valve is emphasized.

AUTHORS.

Gelfman, R., and Levine, S. A.: The Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease. *Am. J. M. Sc.* 204: 324, 1942.

The protocols of four Boston hospitals were reviewed to determine the incidence of acute and subacute bacterial endocarditis and endarteritis among congenital cardiac defects. Special attention was paid to sex, age at time of death, type of cardiac defect and superimposed rheumatic infection.

In 34,023 autopsies, 453 (1.3 per cent) contained significant congenital cardiac defects, 181 of which (40 per cent of the 453) were in patients over the age of 2 years.

Evidence of bacterial endocarditis was present in 6.5 per cent of the 453 cases and in 16.5 per cent of the 181 cases over 2 years of age.

The distribution of males and females was in a proportion of 3 to 2 in both the total group with cardiac defects and in those who showed infectious endocarditis.

Sixty per cent of the patients died before the age of 2 years. For the rest, no predominance was shown in any one age group. The highest incidence of bacterial endocarditis fell in the second and third decades.

Twenty-five (14 per cent) of the 181 hearts with congenital defects were further complicated by rheumatic infection. Congenital bicuspid aortic valve and interauricular septal defects were the most frequent underlying cardiac anomalies, and subacute bacterial endocarditis was present in 8 of these 25 rheumatic hearts.

The incidence of bacterial endocarditis in the most significant cardiac defects was as follows: interauricular septal defects, none; interventricular septal defects, 42 per cent of all and 57 per cent of the uncomplicated cases over 2 years of age; patent ductus arteriosus, 28.6 per cent of all and 20 per cent of the uncomplicated cases over 2 years of age; bicuspid valves, 17.4 per cent of all and 21 per cent of those over 2 years of age; tetralogy of Fallot, 12.5 per cent of all and 29 per cent of those over 2 years of age; pulmonic stenosis, 19 per cent of all and 29 per cent of those over 2 years of age.

AUTHORS.

Lev, M., and Strauss, S.: Stenosis of the Infundibulum. *Arch. Int. Med.* 70: 52, 1942.

A case of infundibular stenosis without transposition is presented from the clinical and the pathologic standpoint. The various types of infundibular stenosis are discussed, and the various theories concerning the pathogenesis of this anomaly are reviewed.

Infundibular stenosis is most frequently part of a tetralogy of Fallot and as such represents the result of an abnormality both in the absorption of the bulbus and in its incorporation into the right ventricle. When stenosis is present without transposition, the absorption of the bulbus must have proceeded normally but its final incorporation into the right ventricle must have been faulty.

AUTHORS.

Foster, D. B.: Association Between Convulsive Seizures and Rheumatic Heart Disease. *Arch. Neurol. & Psychiat.* 47: 254, 1942.

An attempt is made to determine whether rheumatic heart disease is of etiologic significance in the production of convulsive seizures. The study is based on a review of 2,153 patients presenting both conditions. It is concluded that the rheumatic state is of etiologic significance in the production of certain convulsive disorders. This is based on the following facts. The incidence of seizures in rheumatic patients is higher than in the general population. The age onset of seizures in patients with rheumatic heart disease is different from that of the general population. Acute rheumatic fever or Sydenham's chorea preceded the onset of convulsive manifestations in 58.6 per cent of 29 patients; in 34.4 per cent the relation was doubtful, and in 6.8 per cent the convulsive seizures preceded the acute rheumatic infection. A familial incidence of convulsive seizures or migraine appears in the cases of rheumatic heart disease with seizures six times as frequently as in cases of rheumatic heart disease without seizures.

Several mechanisms may be operative in the rheumatic state capable of producing seizures in predisposed patients: paroxysmal cardiac arrhythmia, cerebral passive congestion, delayed auriculoventricular conduction, with or without the superimposition of digitalis, cerebral infarction, and possibly others.

KERSHBAUM.

Hoffman, G. L., Jr., and Jeffers, W. A.: Rheumatic Heart Disease Complicating Pregnancy. A Study of 61 Fatalities. *Am. J. M. Sc.* 204: 157, 1942.

Sixty-one maternal deaths due to rheumatic heart disease in Philadelphia during the past decade have been studied in reference to their preventability, manner of death and certain factors influencing the deaths.

Analysis of the manner in which death occurred among the cases studied indicated that the fatalities due to this disease resulted principally from congestive heart failure following delivery at, or near term.

Of the factors influencing death, the most important one amenable to control was the cardiac status of the patient at the time of delivery. Since this is almost solely dependent upon prenatal care, a significant decrease in the number of maternal deaths due to rheumatic heart disease can only be attained through an improvement in this care.

AUTHORS.

Pearce, John Musser: Susceptibility of the Heart of the Rabbit to Specific Infection in Viral Diseases. *Arch. Path.* 34: 319, 1942.

The intratesticular inoculation of vaccine, pseudorabies, inflammatory fibroma, strain A fibroma and myxoma viruses into rabbits which had been prepared by a preceding intravenous injection of a solution of acacia was followed by the appearance of cardiac lesions in the majority of the animals. Cardiac lesions did not occur or were of minor intensity in animals which had not had a preceding intravenous injection of the solution of acacia. In this respect the action of these viruses in localizing in the heart is similar to that previously described for virus III.

The lesions, regardless of the specific etiologic agent, were situated predominantly in the myocardium, but the viruses which are more prone to engender necrosis and exudation, i.e., vaccine virus and the viruses of pseudorabies and inflammatory fibroma, occasionally produced inflammation of the auriculoventricular valves.

The reaction in the heart was as a rule typical of the agent causing it. Thus in the acute exudative lesion of pseudorabies the intranuclear inclusion bodies

were seen. The myxoma virus induced proliferation of the typical large myxomatous cells, and the fibroma virus that of the characteristic fibroblasts, in the interstices of the heart muscle. The vaccine and inflammatory fibroma viruses brought about a less specific picture of muscle necrosis and leukocytic exudation.

AUTHOR.

Herbut, Peter A., and Maisel, Albert L.: Secondary Tumors of the Heart. *Arch. Path.* 34: 358, 1942.

Thirty-five cases of secondary cancer of the heart are presented. The salient pathologic and clinical features are described, and an attempt at correlation of the two is made. In none of the cases in this series was the cardiac metastasis diagnosed before death.

AUTHOR.

Bruger, M., and Rosenkrantz, J. A.: Arteriosclerosis and Hypothyroidism: Observations on Their Possible Interrelationship. *J. Clin. Endocrinol.* 2: 176, 1942.

The possible relationship between arteriosclerosis and the activity of the thyroid gland was investigated in subjects 55 years of age or older. The basal metabolic rate was correlated with the presence or absence of arterio-sclerosis according to clinical criteria. It was found that the incidence of hypometabolism is greater for those exhibiting arteriosclerosis than for those without arterio-sclerotic manifestations.

KEESBRAUM.

Horn, Henry, Klemperer, Paul, and Steinberg, Morris F.: Vascular Phase of Chronic Diffuse Glomerulonephritis: A Clinicopathologic Study. *Arch. Int. Med.* 70: 260, 1942.

A series of 49 consecutive cases of chronic diffuse glomerulonephritis was investigated, with especial attention focused on the character of the arterial changes in all viscera. An independent and thorough evaluation of the clinical data in these same cases was also made.

In accordance with the varied vascular pictures a division of the disease into a slowly progressive and an accelerated phase is proposed, 14 cases representing the former and 35 cases the latter.

The histologic vascular lesions peculiar to each group of cases are described in detail. The intimal fibrosis, elastosis of arteries and arteriolar hyalinization which were characteristic vascular alterations in the slowly progressive group were also observed in the other groups. A transitional group, in addition, exhibited cellular proliferation, foam cells and edema of the arterial intima, while the advanced accelerated group revealed an even more conspicuous cellular intimal proliferation of the arterial tree and, in addition, distinct necrosis of the arteriolar walls.

A correlation of the clinicopathologic features was then determined. In the majority of cases it was found that the intensity of the clinical picture usually paralleled the anatomic vascular changes.

Neuroretinitis, common in the transitional and the advanced accelerated group, was never observed in cases of the slowly progressive phase of the disease.

On the basis of this survey it is concluded that arterial alterations both in the transitional and in the advanced accelerated groups of cases of chronic diffuse glomerulonephritis represent the anatomic equivalents of the clinical picture which has been designated malignant hypertension. This has been shown to occur more frequently than hitherto suspected in chronic diffuse glomerulonephritis.

In view of the constancy of severe hypertension in a miscellaneous group of diseases in which accelerated arterial changes are present, this factor is considered a potent etiologic force in their production. Whether hypertension is the basic determinant for the appearance of the vascular lesion or is itself mediated through the liberation of a toxic vasopressor substance is beyond the scope of this presentation.

The tempo of the clinical course in instances of chronic diffuse glomerulonephritis may be influenced not only by the exacerbation of the inflammatory process but by the height of the blood pressure.

The occurrence of severe hypertension and neuroretinopathy in disease entities of varied pathogenetic background vitiates the belief that these criteria may be of differential diagnostic import.

The vascular lesions once established contribute importantly to the advancement of the renal process and the intensification of the clinical picture.

AUTHORS.

Shure, Norman M.: Pyelonephritis and Hypertension: A Study of Their Relation in 11,898 Necropsies. *Arch. Int. Med.* 70: 284, 1942.

The incidence of hypertension in patients with pyelonephritis was studied from 11,898 autopsies performed in a ten-year period. In these the incidence was 44.4 per cent as compared to 34.9 per cent in a control group selected at random. In an analysis, however, this greater incidence apparently occurred in patients with bilateral pyelonephritis, especially in the male sex, and was most marked in men over 40. The relative absence of high blood pressure in patients with unilateral pyelonephritis was striking. The incidence of hypertension increased with the age of the patient and was parallel to the incidence of marked renal vascular damage. In small groups of patients with polycystic kidney, horseshoe kidney and uncomplicated nephrolithiasis the incidence of hypertension was 46.15, 64.7 and 53.25 per cent respectively.

AUTHOR.

Bellis, C. J.: The Portal Venous Pressure in Man. *Proc. Soc. Exper. Biol. & Med.* 50: 258, 1942.

The portal venous pressure was determined at laparotomy by inserting a needle, which was attached to a manometer filled with saline, into an omental vein; at the same time, with a similar apparatus, the ankle venous pressure was determined. In sixteen cases the average normal portal pressure was 10 cm. saline higher than the average normal ankle venous pressure. Normal portal pressures ranged between 14 and 22 cm. saline and normal ankle pressures ranged between 5 and 12 cm. saline. In a case of advanced portal cirrhosis with ascites, the portal venous pressure was 40 cm. saline, the ankle venous pressure 8 cm. saline, a difference of 32 cm. saline.

WILLIAMS.

Bean, W.: A Note on the Development of Cutaneous Arterial "Spiders" and Palmar Erythema in Persons With Liver Disease and Their Development Following the Administration of Estrogens. *Am. J. M. Sc.* 204: 251, 1942.

The development of cutaneous arterial "spiders" in 2 of 3 chronic alcohol addicts and palmar erythema in 1, following therapy with potent estrogens suggests that these stigmata of liver disease, pregnancy and deficiency diseases may result from abnormal metabolism of the 17-ketosteroid hormones.

AUTHOR.

Schlossmann, Nathaniel Charles: Fibrinoid Necrosis in Arteriosclerosis. Arch. Path. 34: 365, 1942.

Homogeneous masses exhibiting the tinctorial behavior of fibrin and located within and on the arteriosclerotic plaques of the aorta and the peripheral vessels were analyzed in an attempt to establish their morphogenesis.

Fibrinoid substance could be clearly differentiated from fibrin by controlled tryptic digestion.

Evidence is submitted to establish the fibrinoid substance in arteriosclerotic vessels as partially necrotic collagen.

AUTHOR.

Mendlowitz, M.: The Digital Blood Flow, Arterial Pressure, and Vascular Resistance in Arterial Hypertension and in Coronary Thrombosis. J. Clin. Investigation 21: 539, 1942.

Methods for calculating the digital blood flow from calorimetric observations have been modified and a method developed for calculating digital vascular resistance.

After vasodilatation produced by warming the body, normal digital blood pressure, blood flow, and vascular resistance were found in patients with neurogenic elevations of blood pressure. A consistent increase in digital vascular resistance and a normal digital blood flow were demonstrated in established essential or renal hypertension. In acute and in malignant hypertension, the digital blood flow may be decreased, and the vascular resistance increased out of proportion to the elevation in blood pressure.

Decrease in digital blood flow and blood pressure, and unchanged vascular resistance were demonstrated in cases of acute coronary occlusion, whether the antecedent blood pressure was normal or elevated.

AUTHOR.

Mendlowitz, M.: The Digital Circulation in Peripheral Vascular Diseases. J. Clin. Investigation 21: 547, 1942.

The digital circulation was studied in Raynaud's syndrome, scleroderma, and thromboangiitis obliterans.

In Raynaud's disease and in scleroderma, the digital blood flow is usually decreased and the digital vascular resistance increased. In thromboangiitis obliterans, the digital blood flow is decreased because of a decrease in digital arterial blood pressure, the digital vascular resistance remaining comparatively unchanged.

Study of the digital circulation may be useful as an aid in diagnosis and prognosis, and as an index of the effect of therapy in peripheral vascular diseases involving the upper extremities.

AUTHORS.

Chipps, H. D.: Aneurysm of the Coronary Artery. Am. J. M. Sc. 204: 246, 1942.

A case of mycotic embolic aneurysm of the anterior descending branch of the left coronary artery is presented. A review of the literature reveals 45 cases of coronary aneurysm and 9 of aneurysm of mycotic embolic origin. In this instance the source of embolism was a vegetative endocarditis of mitral and aortic valves due to the *Strep. viridans*. Impaction of the infected embolus in the coronary lumen caused not only the development of aneurysm but also coronary occlusion with infarction of the myocardium. The reasons for the rarity of mycotic embolic aneurysms of the coronary arteries are briefly discussed.

AUTHOR.

Gunther, L., Strauss, L., Henstell, H. H., and Engelberg, H.: Intramuscular Pressure. III. The Action of Various Drugs on Patients With Normal Intramuscular and Venous Pressure. *Am. J. M. Sc.* 204: 387, 1942.

Observations on the action of various drugs on intramuscular and venous pressures are shown in normal individuals. The drugs which are mainly pressor in action do not alter intramuscular pressure, whereas inhalations of CO₂, the tetanic state, and particularly the administration of coramine intravenously definitely raise the level of intramuscular pressure. An increase in intramuscular pressure is accompanied by an increase in venous pressure, whereas the reverse was not observed.

AUTHORS.

Gunther, L., Henstell, H. H., Strauss, L., and Engelberg, H.: Intramuscular Pressure. IV. The Venopressor Mechanism During the Course of Surgical Procedures. *Am. J. M. Sc.* 204: 394, 1942.

After 50 minutes of continuous surgery a drop in intramuscular pressure may precede the fall in venous pressure. In half the instances the low level of venous pressure coincided with the initial drop in intramuscular pressure.

When the intramuscular pressure falls and remains low for 50 minutes or longer, a further decrease in venous pressure occurs which reaches its maximum low point concomitantly with the maximum drop in intramuscular pressure.

Intramuscular pressure fell 5 minutes before the shocklike state began and the venous pressure with its full appearance 20 minutes later during a pericardial thoracentesis.

Further evidence is presented which supports Henderson's postulate in that: (a) intramuscular pressure first fails in shocklike states, and (b) with the failure of intramuscular pressure appears a failure in the maintenance of venous pressure and flow.

AUTHORS.

Lands, A. M., and Johnson, W.: Distribution of Body Water Following Hemorrhage. *Proc. Soc. Exper. Biol. & Med.* 49: 123, 1942.

The source of the water which dilutes circulating blood following hemorrhage was investigated by determining changes in the volume of cellular and extracellular water by comparing the volume of sulfocyanide available water both of the whole animal and of some of its organs after hemorrhage with the values obtained from normal animals. Thirty to sixty minutes after injecting sodium sulfocyanide in anesthetized cats a sample of blood was removed for analyses. Fifteen to 26 ml. of blood per kg. of body weight were then removed. Sixty to 120 minutes later another sample of blood was removed for analyses, the animal sacrificed by asphyxia and the tissues of various organs analyzed for sulfocyanide. The experimental findings were inconsistent with the concept which attributes blood dilution to the movement of a lymph-like fluid from interstitial spaces into the blood stream. The volume of sulfocyanide available water increased after hemorrhage. The chloride concentration of serum water decreased in all experiments save one. The total water and sulfocyanide available water content of cardiac muscle, pancreas, pylorus, duodenum, colon, skin and liver increased after hemorrhage. No significant differences were found in the gastrocnemius muscle and diaphragm.

WILLIAMS.

Hubbard, J. P., Preston, W. N., and Ross, R. A.: The Velocity of Blood Flow in Infants and Young Children, Determined by Radioactive Sodium. *J. Clin. Investigation* 21: 613, 1942.

The velocity of the blood flow in young infants and children has been measured by determining the time elapsed between the injection of radioactive sodium into

one arm and its arrival in the opposite hand. The latter has been signaled by a Geiger counter.

By this method the rate in 22 children between 2 and 12 years was found to average 11 seconds, with a range of 5 to 17 seconds. The rate of 14 infants between 6 weeks and 22 months of age averaged 7 seconds, with a range of 3 to 12 seconds.

AUTHORS.

Lascano, E. F.: The Normal Irrigation (Blood Supply) of the Keith-Flack Node.

Rev. argent. de cardio. 9: 17, 1942.

By means of infections of colored gelatin it has been found that the node of Keith and Flack is always irrigated by a single auricular artery which may be the anterior, lateral or posterior auricular, ascendant branches of the right or left circumflex artery. The artery which irrigates the sinus node is prominent between the auricular arteries and sends to the superior vena cava a large collateral which divides into two branches: an anterior or precava and a posterior branch or retrocava which form—depending on the establishment or not of anastomosis—a ring or half ring around the lower part of the superior vena cava.

If the artery of the node is the right anterior auricular, or the right lateral running anteriorly or the left anterior, lateral or posterior, the collateral which will form the ring or half ring around the superior vena cava will reach the vein by its left lateral border (ring of left origin). If, on the other side, the collateral comes from the right lateral auricular artery running posteriorly or from the right posterior auricular artery, it will reach the vein by its right lateral border (ring of right origin). From this ring or half ring an arteriole springs which runs by the sulcus terminalis, and which appears to be the real nourishing artery of the sinus block.

Constant interauricular communications have been found of a diameter of about 50 microns. These are specially frequent around the superior vena cava, in the anterior aspect of both auricles and in the posterior aspect of the left auricle. They connect both auricular arteries, right and left and sometimes they establish communications between branches of one of the coronary arteries or even of one of the auricular arteries.

In a few cases a strong ring is formed around the cava by the free anastomosis of the two pre and retro cava branches; but smaller pericaval rings formed by anastomosis of finer collaterals of those branches is a constant finding.

AUTHOR.

Davis, H. A., Eaton, A. G., and Williamson, J.: Transfusion of Bovine Serum Albumin Into Human Beings. *Proc. Soc. Exper. Biol. & Med.* 49: 96, 1942.

The effect of transfusion of bovine serum albumin into human beings was determined in 13 subjects. The serum albumin was administered by vein in amounts of 50 to 300 c.c. at a rate of 5 c.c. per minute. Preliminary cross-matching was not carried out. The blood pressure was maintained at, or rose above the initial level. Vasodepression was not observed and no reactions were noted. In view of the encouraging results, the use of bovine serum albumin as a blood substitute in human beings was discussed.

KERSHBAUM.

Prinzmetal, M., Alles, G. A., Margoles, C., Kayland, S., and Davis, D. S.: Effects on Arterial Hypertension of Heat-Inactivated Tyrosinase Preparations. *Proc. Soc. Exper. Biol. & Med.* 50: 288, 1942.

Mushroom tyrosinase preparations were heated to destroy about 95 per cent of their enzymic activity. These heat-inactivated tyrosinase preparations can produce significant lowering of blood pressure and remission of other symptoms

of arterial hypertension in man. The results were as marked as those reported by others using active tyrosinase preparations, which shows that the effect is not related to the enzyme content of the preparation.

WILLIAMS.

Sapirstein, L. A., Southard, F. D., Jr., and Ogden, E.: Restoration of Blood Pressure by Renin Activator After Hemorrhage. *Proc. Soc. Exper. Biol. & Med.* 50: 320, 1942.

Injection of a renin-activator preparation of ox-plasma in dogs, following hemorrhage, produced a very marked rise in blood pressure, which persisted for 20 to 120 minutes. Further injection of the activator preparation during the period of restored blood pressure produced no pressor effect, but after the pressure had fallen to lower levels, whether spontaneously or after further bleeding, renewed injection again produced an increase in blood pressure. The injected renin-activator preparation contained only one-tenth or less of the total plasma protein removed. Corresponding quantities of 10 per cent gelatin or of control plasma concentrations failed to restore the blood pressure. It is concluded that the secretion of renin in severe hemorrhage is sufficient to produce exhaustion of renin activator. The resulting failure of the reno-pressor system is followed by a fatal collapse of blood pressure which may be staved off and the blood pressure restored by replacing the exhausted activator. The possibility of improving transfusion therapy of hemorrhage and shock by fortifying the plasma with preparations of renin-activator, or of substituting small quantities of activator preparations for plasma in emergency treatment, is suggested.

WILLIAMS.

Vermeulen, C., Dragstedt, L. R., Clark, D. E., Julian, O. C., and Allen, J. G.: Effect of the Administration of Lipocaic and Cholesterol in Rabbits. *Arch. Surg.* 44: 260, 1942.

Experiments were undertaken in rabbits to test the possibility that a deficiency in lipocaic production plays a role in the development of vascular disease. The administration of cholesterol orally produced a sustained, hyperlipemia, hypercholesteremia, arteriosclerosis of the aorta and accumulation of cholesterol and fat in excessive amounts in the liver and adrenal glands. The simultaneous oral administration of lipocaic in amounts up to half of the daily requirement of a dog prevents a rise in the noncholesterol fraction of the blood lipids and also the deposition of fat and cholesterol in the liver but has no effect on hypercholesteremia and arteriosclerosis caused by the oral administration of cholesterol.

KERSHBAUM.

Pettus, W. W., Geiger, A. J., and Grzebien, S. T.: Effects of Morphine on the Electrocardiogram of Man, *Yale J. Biol. & Med.* 14: 493, 1942.

The authors studied the effects of morphine on the electrocardiogram in 10 normal subjects and 10 patients with coronary artery disease. Doses up to $\frac{1}{2}$ grain were used hypodermically, and both limb and chest leads were taken. No striking bradycardia was generally observed, as is frequently seen in animal experiments. Shift of the pacemaker and premature beats each occurred once in these experiments. The drug did not significantly alter either the initial or final portion of the ventricular complex. It is concluded that the administration of the drug would probably not cause confusion in the electrocardiographic diagnosis of acute myocardial injury in man.

KERSHBAUM.

Myerson, A., Rinkel, M., Loman, J., and Ritvo, M.: *The Prolonged Effect of Amphetamine Sulphate in Gelatin.* *Am. J. M. Sc.* 204: 254, 1942.

The following comparative effects of amphetamine-gelatin mixture and aqueous amphetamine solution were observed:

Circulatory System: The increase in blood pressure and the corresponding decrease in pulse rate produced by amphetamine was not delayed or prolonged when the drug was dissolved in gelatin.

Gastrointestinal System: There was a definite prolongation of the characteristic effects of amphetamine sulphate (decrease in tone and peristalsis) when the drug was mixed with gelatin. This action was observed in man following roentgen ray studies, and in animals by direct observation of the gastrointestinal tract.

The delay in absorption of alcohol which follows the administration of amphetamine sulphate is definitely more marked when the drug is mixed with gelatin.

AUTHORS.

Darrow, D. C., and Miller, H. C.: *The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate.* *J. Clin. Investigation* 21: 601, 1942.

Necrosis of the myocardial fibers and replacement by fibroblasts is produced by repeated injections of desoxycorticosterone acetate in rats. The lesions are neither aggravated by absence of pyridoxin nor prevented by liberal additions of pyridoxin to the diets. Low intake of thiamin does not aggravate the lesion. The lesions cannot be distinguished from those produced by diets low in potassium. The livers decrease in size after injections of desoxycorticosterone acetate for 10 days, but are normal in size after 4 weeks of injections.

The injection of desoxycorticosterone acetate lowers muscle potassium and raises muscle sodium. Analogous changes are not found in the liver. Low cardiac potassium was found in the heart in 2 of 4 dogs fed a diet low in potassium. Injection of desoxycorticosterone produced only suggestive lowering of cardiac potassium in a group of rats, no certain change in any of 4 cats, and no change in 1 dog. Although the heart may lose potassium under conditions leading to loss from skeletal muscle, diminution of cardiac potassium is not a regular occurrence.

The cardiac lesions produced by injections of desoxycorticosterone acetate or diets low in potassium can be prevented by addition of potassium chloride to the drinking water. Deficit of body potassium is apparently essential for the production of these lesions.

Cortical extract produced analogous changes in the muscle of the one rat.

AUTHORS.

Book Review

LA DIGITAL: By Dr. Alejandro Garretón Silva, Professor of Medicine, University of Chile. Empresa Editora Zig Zag, Santiago de Chile, 1941, 143 pages.

This booklet reviews old and recent studies on the pharmacology and clinical use of digitalis. Some North American contributions, such as the method of standardization of digitalis on man described by Gold, and the changes incorporated in the United States Pharmacopoeia XII, are not included. The book does not add anything to existing knowledge concerning digitalis, but it should be useful to Spanish practitioners, for whom it was apparently designed.

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estimations were made. While in this anoxic state, contractions during ischemia were made in the usual manner. There was absolutely no change in the amount of work that could be done under these extreme conditions. As a matter of fact, the strongest evidence that anoxia was not a factor was the prompt disappearance of pain when the circulation was restored, while the subject was still anoxemic and dyspneic.

VII. Remote and Reflex Secondary Effects of Ischemic Work.—One of our earlier observations on exercise during ischemia was that, with occlusive pressures of 140 to 180 mm. Hg, oscillations of low amplitude could be seen in the mercury column before any signs of pain had appeared. These oscillations meant that there was some flow of blood under the constricting cuff. Normally, the systolic pressures of these subjects ranged from 110 to 130 mm. Hg. After several trials had shown that no oscillations occurred at 200 mm. Hg, this level was chosen as the occluding pressure. These observations led us to study the blood pressure before and after work during ischemia, and striking and interesting changes were found. The following case illustrates this point:

(24C) Normal B.P.	120/86
After work during ischemia* (40 contractions)	170/110
On release of occlusion	130/90
1½ minutes after release	120/90
2 minutes after release	120/86

Even exercise of one finger during ischemia, in this case the little finger, caused an appreciable rise in pressure:

(25D) Normal B.P.	118/80
After work during ischemia (90 contractions)	136/90

Both the systolic and diastolic pressures are affected. In contrast, simple ischemia results only in a minimal systolic rise (4 to 6 mm. Hg). Restoration of the circulation causes not only prompt disappearance of muscle pain and ache, but also return of the blood pressure to its resting level. Both changes take place with the appearance of reactive hyperemia.

The pulse rate, even when work was done during ischemia, tended to remain unchanged. However, after restoration of the circulation, there was a fall of 5 to 10 beats in some instances. Variations in the size of the pupils were too small to allow us to ascertain whether adrenalin was released by reflex stimulation of the adrenal glands.

VIII. Pain Originating in Nonmuscular Tissues.—In the following group of experiments we attempted to study pain from nonmuscular tissues, and the factors affecting its production. The procedure was the same as that outlined under "Method of Study," except that the finger, rather than the entire limb, was used for testing; the finger was taken to represent a nonmuscular organ.

*Taken on nonoccluded side, of course.

RESULTS

I. Influence of Muscular Exercise Prior to Circulatory Arrest.—

1. Local exercise has a profound influence upon the ability to carry out work during ischemia. Forty vigorous flexion and extension movements of the fingers were made, followed by circulatory arrest and then work in the usual manner. The result was clear cut and conclusive: perhaps $\frac{1}{3}$ to $\frac{1}{2}$ of the usual number of contractions could be made, i.e., only 16 contractions were possible for a person who had been consistently capable of making 40 such motions. This confirms the results originally obtained by Lewis, et al.¹

2. Exercise of the whole body also tends to diminish the amount of work that can be carried out subsequently by an ischemic limb. After stationary running movements at a good rate for 5 minutes, fewer contractions were possible (34 for a person who usually made 40 contractions). Because the total amount of work done in running is unquestionably more than that done by an arm alone, some explanation for the quantitative difference between local and general exercise must be made.

II. Nontransferability of Pain From Lower to Upper Extremities.—

Cuffs were applied to both legs above the knee. The subject performed work during ischemia by flexing and extending both feet. Sixty contractions were made before pain caused a halt. Both cuffs were then deflated to permit free blood flow for 40 seconds, during which time the blood from the exercised regions entered the general circulation. Thus blood from the legs eventually reached the upper extremities in less than two complete circuits around the body. A cuff was then applied to one of the arms, and work was done in the usual manner. The number of contractions was identical with the normal number, indicating clearly the lack of influence of the preceding exercise.

*III. Phase of Recovery.—*Restoration of the circulation invariably results in almost instantaneous and complete disappearance of pain.¹ At the same time, the bright pink flush of reactive hyperemia and a feeling of warmth distal to the point of occlusion appear. Paresthesias, such as tingling and "pins and needles" sensation, become quite prominent in the fingers; they persist for a variable period of minutes.

The relationship of the phase of recovery to the amount of work that is possible during ischemia is best illustrated by an experiment of this nature: An ischemic limb, which was capable of performing 40 contractions, had its circulation restored for 15 seconds, followed by rearrest and exercise. Only 11 contractions were possible before the appearance of disabling pain. With restoration of the circulation for one minute, 17 contractions could be made; for two minutes, 22; for three minutes, 34; and, for 5 minutes, 44, which was the maximum number. Inasmuch as the same results occurred regularly in different subjects, we became convinced that, with a minimum of three minutes, and certainly of five minutes, the working muscles recover sufficiently to be able to do the basic amount of work during ischemia. This interval

was therefore taken in subsequent experiments as the time needed for reversal of the fatigue and pain process.

Incomplete restoration of the circulation has a rather curious effect. The pressure in the cuff is reduced by stages of 10 mm. Hg. Almost complete relief of pain is obtained at 150 mm. Hg (it will later be shown that the systemic pressure is elevated by activity during ischemia; in this case, blood inflow occurs at 150 mm. Hg). Within a few seconds, however, the pain reappears in full force and is, by contrast, even more painful and vise-like than before. If the pressure is dropped further, relief is again experienced, only to have the pain return once more. At 120 to 130 mm. Hg, only a feeling of heaviness and fatigue exists. At this point the skin is lividly hyperemic. The pain disappears completely at 80 mm., which is the diastolic level.

IV. Influence of Temperature on the Ischemic Limb.—If the ischemic extremity is heated by immersion in a water bath at a temperature of 115° F., a feeling of fatigue, disinclination to move the part, and, finally, cramplike pain in the wrist and muscles of the forearm develop. The pain in the wrist is especially severe, and occasionally the arm has to be withdrawn, so intense does it become. These sensations begin shortly after exposure to heat and are intense in from five to thirteen minutes; the time variations are dependent, in our estimation, on the insulation of the limb, i.e., a thick arm, with much subcutaneous fat, requires more time for heat to penetrate to the musculature than a thinner extremity. In all probability this is the reason why pain is felt so intensely in a superficial region like the wrist. Removing the arm from the bath decreases the intensity of the pain but does not relieve it completely; this is possible only with restoration of the circulation. The pain in the muscles is similar to that caused by work during ischemia, but is not as severe nor does it reach its peak as rapidly. These sensations are in marked contrast to what happens with simple arrest of the circulation.

Subjecting the arm to a lowered temperature by immersion in water at 60° F. caused no pain or paresthesias even after fifteen minutes of exposure. The only noticeable effects were a feeling of fatigue in the flexor muscles of the forearm and the rather marked cadaveric lividity of the skin.

If the ischemic arm is heated at 110° F. until stiffness and aching occur in the muscles of the forearm, and, at this point, it is called upon to work as in previous experiments, fewer contractions are possible before intolerable pain is reached. In one instance (KH) only 31 contractions could be made; in another (IDS), only 32. Each of these subjects was capable of making 38 to 42 contractions during ischemia, without heating. The reverse holds true with cooling; the number of contractions that are possible before reaching the end point is definitely greater; in other words, the pain process is retarded.

V. Influence of Vasodilatation.—The possibility that ischemic pain might be caused by excessive stretching of the arterioles and finer sub-

divisions of the arterial tree as a result of the vasodilatation which regularly accompanies circulatory arrest in a limb has been suggested.⁷ In order to avoid the effects of changing the temperature, which is the usual method of producing active hyperemia, we employed reactive hyperemia (Grant and Pickering) and reflex hyperemia (Landis and Gibbons). Neither of these methods, in contrast to heating directly, increases tissue metabolism.

To produce reactive hyperemia, in an arm in which the circulation had been occluded for 10 minutes, the circulation was restored, and, as the hyperemia reached its maximum (in from a few to twenty seconds), the circulation was rearrested and work begun. Repeated observations showed that the capacity for work remained unchanged; 38 to 40 contractions could still be made when vasodilatation was present.

To bring about reflex hyperemia, both legs were immersed in a water bath at 110° F. while the circulation in one arm was arrested. Within 20 minutes there was a rise in the temperature of the forefinger on the nonoccluded side from 75° F. to 95.5° F. Inasmuch as such a temperature rise is the maximum, vasodilatation in the extremities should have been complete. Yet there was no pain in the occluded limb, and the number of muscle contractions during ischemia was 37, which was nearly normal for this subject. The length of the period of occlusion—twenty minutes—may well have produced a slight diminution of the exercise tolerance.

VI. Influence of Oxygen.—Whether diminution of the oxygen supply to the working tissues is the cause of ischemic pain has been the subject of much controversy. Lewis, et al.,¹ showed that simple circulatory arrest for fifteen to twenty minutes would produce anoxemia without any painful sensation, and that, if work was attempted at this time, there was no reduction in the number of contractions, in spite of the marked oxygen lack. They went even further to substantiate this statement by showing that, if work during ischemia was halted short of the point at which intolerable pain was reached, the circulation could be kept occluded for many more minutes without the development of pain. Obviously, the muscle exercise must have made tremendous inroads on the amount of oxygen available, as did also the following period, during which arrest was maintained without work. Yet there was no pain. Other workers, notably, Kissin,⁴ feel that oxygen lack is the main cause of ischemic pain. Kissin showed that, in a group of normal persons, muscle exercise in a reduced oxygen atmosphere without arrest of the circulation hastened the development of pain. To clear up this problem, the authors conducted the following experiments on each other.

A mixture of 10 per cent oxygen and 90 per cent nitrogen was led into the breathing bag of a Gwathmey anesthesia machine. The gas was breathed and rebreathed from this closed system by regular respiratory movements; within two to four minutes the subjects became extremely cyanotic and dyspneic. The final value for oxygen in the mixture must have been exceedingly low, although no quantitative

estimations were made. While in this anoxic state, contractions during ischemia were made in the usual manner. There was absolutely no change in the amount of work that could be done under these extreme conditions. As a matter of fact, the strongest evidence that anoxia was not a factor was the prompt disappearance of pain when the circulation was restored, while the subject was still anoxic and dyspneic.

VII. Remote and Reflex Secondary Effects of Ischemic Work. One of our earlier observations on exercise during ischemia was that, with occlusive pressures of 140 to 180 mm. Hg, oscillations of low amplitude could be seen in the mercury column before any signs of pain had appeared. These oscillations meant that there was some flow of blood under the constricting cuff. Normally, the systolic pressure of these subjects ranged from 110 to 130 mm. Hg. After several trials had shown that no oscillations occurred at 200 mm. Hg, this level was chosen as the occluding pressure. These observations led us to study the blood pressure before and after work during ischemia, and striking and interesting changes were found. The following case illustrates this point:

(230) Normal B.P.	127/86
After work during ischemia*	126/66
100 contractions	
On release of occlusion	127/72
1½ minutes after release	127/70
2 minutes after release	127/80

Even exercise of one finger during ischemia, in this case, the little finger, caused an appreciable rise in pressure:

(250) Normal B.P.	118/80
After work during ischemia	127/70
100 contractions	

Both the systolic and diastolic pressures are affected. In contrast, simple ischemia results only in a minimal systolic rise (4 to 6 mm. Hg). Restoration of the circulation causes not only prompt disappearance of muscle pain and ache, but also return of the blood pressure to its resting level. Both changes take place with the appearance of reactive hyperemia.

The pulse rate, even when work was done during ischemia, tended to remain unchanged. However, after restoration of the circulation, there was a fall of 5 to 10 beats in some instances. Variations in the size of the pupils were too small to allow us to ascertain whether adrenalin was released by reflex stimulation of the adrenal glands.

VIII. Pain Originating in Nonmuscular Tissues.—In the following group of experiments we attempted to study pain from nonmuscular tissues, and the factors affecting its production. The procedure was the same as that outlined under "Method of Study," except that the finger, rather than the entire limb, was used for testing; the finger was taken to represent a nonmuscular organ.

*Taken on nonoccluded side, of course.

Immersing it into water at a temperature of 115° F. resulted, within one minute, in a stinging and stabbing type of pain which increased rapidly so that, in another thirty to sixty seconds, the sensation became very unpleasant. Some relief was brought about by removing it from the bath. Re-immersing the finger at this time caused the pain to appear even more quickly.

Cooling the ischemic finger in ice water did not result in any painful sensation.

In these respects, the fingers respond like the muscles of the forearm, except for the nature of the pain and the rapidity of its onset.

A finger treated by histamine or mecholyl iontophoresis becomes hyperemic. This finger responds in the usual way to heating and cooling when the arm is made ischemic, that is, pain appears in 1½ to 2 minutes in the one instance, and not in the other. If the finger is treated with adrenalin by the same method of ion transfer, it becomes blanched because the superficial vessels are constricted. When heat is now applied, almost immediately there is severe, stabbing pain which necessitates immediate removal of the finger. Even with the circulation normal, the adrenalin-treated finger, when immersed in hot water, becomes exceedingly painful, although not quite as much so as if circulatory arrest were present. The reaction occurs only if the finger is exposed to heating; otherwise, there is no pain in the blanched finger.

These facts make it clear that the pain of ischemia is not limited to muscular tissue; it may also arise from the ischemic skin (and probably to some extent from subcutaneous tissue). The pain which originates in ischemic skin differs from that arising in the muscle. Whether this difference can be attributed to the type of sensory end organ concerned, and whether the cause of the pain is the same in both instances are questions which cannot be answered with any degree of certainty at this time.

DISCUSSION

A most plausible explanation of ischemic pain has been advanced by Lewis, et al.¹ It lays emphasis on the muscular activity by which the metabolites responsible for the pain are elaborated, and on the circulatory stasis which creates the physical condition that permits these metabolites to accumulate in the cells and tissue interspaces, where they may reach a concentration sufficient to irritate or stimulate the sensory end organs. This substance or group of substances has been designated by Lewis as the *pain factor*, or *P factor*. Although it has not been isolated or even identified, clinical observations by others, as well as ourselves, lend support to the possibility that it exists. Muscular activity during ischemia, when viewed in this light, means an increase of the *P factor* to the level of pain production. Mention has been made of the effect of muscular work prior to circulatory arrest. Local exercise (of the upper extremity) greatly curtails the amount of work that is possible during ischemia; general exercise shortens it to a lesser extent. Superficially,

these facts seem inconsistent because the total amount of work done during vigorous exercise is unquestionably greater than during exercise of the arm alone. The difference is readily explained. P factor is produced in each case, but, after local work, even with the circulation normal, some must still be retained in the tissues of the arm. With subsequent contractions during ischemia the threshold level is therefore reached sooner, i.e., with fewer contractions. After vigorous body exercise, however, before blood from the exercised regions reaches the muscles of the forearm, the P factor contained in the arm has been dissipated or destroyed to such an extent that it can be of minor importance only, i.e., produce a diminution of only 6 to 8 contractions. It is the concentration of P factor at the place of activity which determines the onset and intensity of pain, not the P factor produced at some more remote area. This also explains the nontransferability of pain from the lower to the upper extremities.

The influence of temperature changes on the ischemic limb has been presented. Ordinarily, in such an extremity there would be no pain even after twenty to thirty minutes of circulatory arrest. But heating increases the metabolic activities of the tissues, augments the production of metabolites, and causes pain to appear. This may be increased by concomitant muscular exercise, so that the combination of both types of activity allows fewer contractions during ischemia. Just the reverse is true when the limb is cooled, i.e., there is a retardation of the pain process. The similarity between the pain produced by exercise and that produced by heating the forearm has already been discussed. They appear to differ only in the rapidity of onset and in intensity. This has been ascribed to the total increase in tissue metabolism, which is much faster with muscular exercise. Environmental changes may therefore influence the rate of production of the P substance, and, under the proper ischemic conditions, may help it accumulate to the effective pain level.

The effect of temperature has some clinical bearing. In the treatment of peripheral vascular disease it has been stressed time and time again that heating a limb with impaired circulation is not without inherent danger. It is common experience that, after some forms of heat treatment, the patient may complain of increased pain.⁸ An adequate explanation for the pain after such treatment is the impetus it gives to the formation of P substance; disease of the vascular tree has produced partial ischemia of the limb. Cooling has been used clinically to diminish tissue metabolism and thus pain sensation. The inconvenience of this mode of treatment and certain undesirable side reactions preclude its general acceptance.

That painful sensation may originate in nonmuscular tissues under certain conditions of circulatory arrest and increase in metabolic activity has been demonstrated. As we pointed out in a previous communication,⁹ the simple assumption that pain is caused by accumulation of heat in the ischemic tissues is not tenable. The striking effect

of a topical application of adrenalin militates against this theory. It can only constrict the surface vessels, without altering the physical properties of the finger. One is forced to assume that this sensation represents true ischemic pain in the skin. Its nature is different from that produced by muscular work during ischemia. Instead of being dull, aching, and rather difficult to localize, it is sharp, stinging, and stabbing in nature, and is referred directly to the offending area. The difference may be accounted for by the difference in the character of the sensory end organs in the two regions. Clinically, one meets with the same phenomenon. In intermittent claudication the pain is dull and aching in character, and is referred to the calves or the ankles; with superficial necrosis it is sharp, stinging, burning, or stabbing, and is referred directly to the toe.

Relief from pain is obtained by restoration of the blood flow. Without this, such alternatives as stopping exercise or removing the source of heat cannot suffice for any appreciable period. Partial removal of the obstruction to blood flow has the same effect; the pain is relieved for a short time, only to return with increased intensity until the circulation is completely restored. The minimum time required for reversal of the pain process in the phase of recovery is at least three minutes. During this period, resumption of blood flow washes away or destroys enough P factor in the region of the nerve endings so that the usual amount of work during ischemia may be repeated.

Among the theories as to the cause of ischemic pain have been two opposing ones, namely, excessive vasoconstriction and excessive vasodilatation. The basis for the first theory is probably the analogy between the vasospasm (and pain) induced by cold in Raynaud's syndrome, and the fall in tissue temperature produced by circulatory arrest. Lewis, et al.,¹ showed conclusively, as did Rein and Schneider,¹⁰ that vasodilatation regularly occurs distal to the point of occlusion, and is probably due to the local effect of metabolites (lactic acid, CO₂, histamine, acetylcholine, adenosine-phosphoric acid). This fact and the lack of effect of reactive hyperemia and reflex hyperemia certainly cast great doubt on the validity of both theories. Even more conclusive was the effect of injecting vasodilating substances into the arterial tree. Although intense hyperemia resulted, it was unaccompanied by any semblance of pain. These observations will be presented in a later paper.

The much disputed role of oxygen in relation to the development of ischemic pain was touched upon. Lewis held that the oxygen content of the blood is not primarily responsible for the pain; later work by Kissin⁴ tended to disprove this, and his statement carries some weight to the present day. The extreme anoxic states reached in the course of these experiments and the lack of influence on the tolerance to activity during ischemia would seem to confirm the original view of Lewis.

Finally, a word must be said about the changes in blood pressure and pulse rate which occur with exercise during ischemia. A fairly

marked rise in both systolic and diastolic levels is observed long before the pain threshold is reached, so that it cannot be the result of the pain. The pulse and respiratory rates are only slightly increased. Reid⁶ noticed the same phenomena in his studies on the effects of simple ischemia. He thought that the precipitate fall in blood pressure to the usual level, or even below, when the blood flow was restored was caused by "the sudden release of the products of metabolism . . . and the sudden cessation of afferent impulses with removal of pain . . ." Alam and Smirk¹¹ felt that the blood pressure rise was caused by passage of nerve impulses from the exercised muscle to the vasomotor center. The stimulus which started the reflex and maintained it during circulatory arrest was the accumulation of muscle metabolites. Since this view fits into the muscle metabolite theory of ischemic pain, we are inclined to favor it; the P factor may indeed be responsible for both mediation and causation of a blood pressure rise, as well as pain. It is possible that a reflex release of adrenalin from the adrenal glands may be the direct cause of the blood pressure elevation. This offers an attractive field for further study.

SUMMARY AND CONCLUSIONS

In a limb whose circulation has been arrested, an increase in tissue activity, whether caused by muscular activity or heating of the tissues, results in painful sensations. Even nonmuscular tissues may be affected in the same process. The relationship of the pain to the so-called P substance has been outlined. Other factors, which appear to exert little or no direct influence, are vasodilatation, vasoconstriction, and the amount of oxygen supply to the tissues.

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STUDIES ON THE NATURE OF PAIN ARISING FROM AN ISCHEMIC LIMB

II. BIOCHEMICAL STUDIES

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THE substance (or substances) responsible for ischemic pain has been designated the *pain factor*, or *P factor*, by Lewis. Some of its properties and the factors which influence its development are already known.^{1, 2} Most important for the purpose of this study, namely, its identification, was the knowledge gained from clinical observations.³ It must be capable of production or mobilization within the one and one-half to two minutes which elapse between occlusion of the circulation and the completion of work during ischemia. It must also be capable of destruction or dispersion by the blood stream in the few seconds which follow restoration of the circulation. Finally, it must revert to its original level in the tissues (and the blood) within the three to five minutes of the recovery phase, after which the muscles can again perform the usual amount of work during ischemia.

METHODS OF STUDY

The only practical method of obtaining information about tissue metabolism in the intact human being is an indirect one, namely, examination of the blood stream for the substances brought to the tissues by the arteries, and the substances elaborated there and removed by the veins. Because the ischemic state obviously precludes transport of substances by way of the arteries, our studies were confined to the venous blood. In another part of this study, several of the suspected substances were introduced intravascularly in an effort to reproduce the pain of ischemia.

Samples of blood were taken from an antecubital vein, without stasis. The first, or *rest*, sample was withdrawn from the control arm with its normal blood circulation. Then the blood flow in the other arm was rapidly cut off by applying a pressure cuff above the bend of the elbow and maintaining a pressure of 200 mm. Hg. Rhythmic extension and flexion of the fingers were performed at a rate of approximately 40 per minute. As soon as intense pain appeared (after 40 to 60 contractions), the needle was inserted into a deep antecubital vein and the cuff quickly deflated. There was a 5- to 10-second wait before the next, or *exercise*, specimen was withdrawn, so that the sample would contain blood from the deeper tissues. The entire time required for collection was usually less than a half minute. A third sample was taken exactly three minutes after restoration of the circulation in the exercised arm. This corresponded to the minimum period required for *recovery*,³ and the specimen was so labelled.

Preliminary steps were begun without delay. Before doing plasma or serum analyses, the samples were recentrifuged to remove all traces of cellular elements.

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I. CHEMICAL STUDIES ON BLOOD

Lactic Acid.—First among the substances to be investigated with respect to the cause of pain was lactic acid. In addition to the fact that it is an important metabolite of muscular activity, its ability to shift the acid-base balance to the acid side had made it a ready target in the search for the hypothetical pain factor. Moore and Moore⁴ made this inference in their work on the pain sensibility of arteries, although there was no attempt to confirm the possibility by actual test. Katz, et al.,² likewise suspected that lactic acid was the substance responsible for ischemic pain.

When blood samples were taken in the manner described and analyzed by the gasometric method of Avery and Hastings,⁵ the results showed clearly that lactic acid could not possibly be the pain factor, in the light of the criteria already outlined.

Representative analyses are shown in Table I.

TABLE I
LACTIC ACID (MG. PER CENT)

CASE	REST	WORK DURING ISCHEMIA	RECOVERY
20C	12.3	29.0	40.7
21C	10.4	28.2	34.2
22A	10.4	28.0	32.6

The increase in lactic acid during the period of recovery, when all trace of pain had disappeared, discredits any claim that it is responsible for the pain. Indeed, we have observed it to increase, as have others,⁶ and to remain elevated for some time after resumption of blood flow, as more of it is "washed out" from the deeper tissues. As for its effect on shifting the acid-base balance, simultaneous estimation of the CO₂ combining power of the blood serum showed that it remained unchanged with this amount of exercise during ischemia. The "out-pouring" of lactic acid must be effectively neutralized. Katz, et al.,² reported that ischemic pain is hastened by acidity and retarded by alkalinity. Their results, however, were obtained by procedures which required inhalation of 10 per cent CO₂ and the ingestion of large amounts of sodium bicarbonate. Such conditions are extreme, and do not pertain to the more physiologic limitations of work. Maisson and Forster,⁷ in studying the pH of intercellular fluid during ischemic muscle contraction by means of a capillary glass electrode inserted into the belly of the working muscle, showed that there was an increase in acidity which reached its maximum many minutes after the circulation had been restored and pain had disappeared. The moderate changes which they observed in the pH of intercellular muscle fluid seem to parallel closely the curve of formation of lactic acid during exercise. Such a degree of acidity obviously does not change the alkali reserve of the blood, as shown by our experiments. At any rate, their results

agree with our contention that neither lactic acid nor a shift in acid-base balance has anything to do with the problem of ischemic pain.

Histamine.—Attention was centered on this substance because Anrep and Barsoum⁸ had claimed that it was liberated during muscle contraction and was responsible for the hyperemia which ensued. Reasoning further along this line, it was conceivable that histamine might be the substance involved in the theory which regards excessive stretching of the vessel walls during vasodilatation⁹ as the cause of ischemic pain. Furthermore, it has already been implicated by Rosenthal and Minard¹⁰ as the cause of pain in the denuded or injured skin.

Blood samples were collected from our normal subjects in the usual manner; the amount of histamine was estimated by Code's modification¹¹ of Barsoum and Gaddum's method, using guinea pig's ileum for assay. Inasmuch as our estimations showed that histamine in whole blood remained unchanged during the course of the experiments, it was thought possible that the expected increase⁸ might be so small that it would be detected earlier in the plasma. Such a search, however, likewise proved fruitless (Table II).

TABLE II
HISTAMINE

CASE	SPECIMEN	REST	WORK DURING ISCHEMIA	RECOVERY
29A	whole blood	0.05 gamma/c.c.	0.04	0.04
30C	whole blood	0.14	0.10	0.10
34A	plasma	—	none*	—
34C	plasma	none*	none*	none*
35A	plasma	none*	none*	none*

*Only minimal, nonspecific contractions obtained.

Inasmuch as the values of histamine were well within the normal range, there is no proof that histamine itself is the pain substance or that the vasodilatation it might produce (in conjunction with other metabolites) results in the painful sensations that arise in ischemic tissues. The discrepancy between our figures and those of Anrep and Barsoum is undoubtedly to be explained by the difference in the nature of the two investigations. They employed dogs, and subjected them to much more muscular work than our subjects accomplished. A recent study by Kwiatkowski¹² substantiates our results; he, too, was unable to find an increase in histamine in either human whole blood or plasma, even after reactive hyperemia.

Many other substances were sought and found wanting, according to our criteria for a possible role in the pain process.

Blood Ammonia.—Embden, et al.,¹³ had shown that ammonia was released from adenosine-phosphoric acid during muscular exercise under pathologic conditions, and possibly also under physiologic ones. It was conceivable that this might be the pain substance, especially since Maison¹⁴ had shown how painful the injection of ammonium salts was.

Analyses were made by the Conway micromethod,¹⁵ and there was no difference in the three samples.

Blood Adrenalin.—According to Bacq,¹⁶ intermediary oxidation products of adrenalin (adrenoxine) have vasodilating and inhibiting actions. McDowall and McWham¹⁷ and others have also shown that adrenalin itself may behave as a vasodilator in muscle. For that reason adrenalin and its oxidation product were estimated by the Shaw modification¹⁸ of the Whitehorn method. Although this method is not entirely satisfactory, the complete absence of any change in adrenalin content was sufficient proof that neither it nor its oxidation products are involved in ischemic pain.

Oxidation Potential.—This was studied because of the possibility that, in the absence of oxygen, incompletely oxidized metabolites which would change the oxidation potential of the tissues and eventually of the blood might be formed. Such changes might be parallel, and indicative of the cause of ischemic pain. The methods employed were both colorimetric (brilliant cresyl blue, methylene blue chloride, sodium 2, 6-dichlorobenzeneindophenol) and potentiometric (Beckman potentiometer, using a blank platinum electrode). Again no appreciable differences could be found in the three samples of blood serum.

Conductivity of Sera.—This might serve as an indicator of the possible alteration of the total electrolyte balance in the blood serum coincident with the appearance and disappearance of ischemic pain. There was no essential change in the three samples, as shown by the Beckman potentiometer.

Serum Potassium.—Potassium was of particular interest in this connection because of its high concentration in muscle cells. It influences many of the fundamental properties of muscular tissues, notably those of irritability and contractility, and participates in a multiplicity of seemingly diverse, remote effects during the intermediary action of adrenalin and acetylcholine. Furthermore, Moore, Moore, and Singleton¹⁹ found that the potassium ion was extremely irritating when injected into the femoral arteries of narcotized cats, and suggested "that accumulation of acid metabolites or potassium ion in inflamed areas is more important to production of pain than increased tissue-tension." The quantitative method employed by us was that of Weichselbaum, Somogyi, and Rusk.²⁰ This proved to be both convenient and accurate. Even small amounts could be estimated, and duplicate and triplicate checks differed by less than one milligram per cent. In other words, the small variations of potassium ion concentration in our experiments were significant. The three standard samples were withdrawn from each one of our subjects and analyzed. As has been stated, all erythrocytes were removed by double centrifuging to obviate any error caused by this factor (Table III).

Potassium proved to be the one substance which was regularly increased by ischemic work, but fell quite promptly to its original level

TABLE III

SERUM POTASSIUM IN VENOUS BLOOD OF NORMAL PERSONS

CASE	CIRC. NORMAL BEFORE EXERCISE	CIRC. OCCLUDED AFTER EXERCISE	CIRC. NORMAL RECOVERY	REMARKS
1	16.5	20.2	15.1	49 contractions
2	14.4	16.8	14.8	50 contractions
3	13.5	18.9	14.6	45 contractions
4	16.7	22.6	16.0	47 contractions
5	21.0	22.7	19.6	39 contractions
6	19.0	22.9	17.6	50 contractions
7	21.8	24.8	19.0	35 contractions
8	20.0	23.6	19.4	46 contractions
9	19.7	22.1	18.4	42 contractions
10	16.7	18.9	15.3	50 contractions
11	17.0	18.7	17.0	35 contractions
12	—*	18.7	16.5	50 contractions
13	14.6	17.2	13.4	55 contractions
14	19.6	24.9	19.3	100 contractions
15	16.9	19.0	16.9	54 contractions
16	19.6	25.0	19.3	38 contractions
17	21.1	23.0	20.9	54 contractions
18	16.5	19.4	16.2	64 contractions
19	18.2	21.2	17.8	65 contractions
20	22.1	24.2	21.7	55 contractions
21	19.2	21.5	18.3	65 contractions
22	17.4	20.0	17.0	55 contractions
23	15.3	18.2	14.8	65 contractions
Average increase			3.0 mg./100 c.c. potassium	
Minimum increase			1.6 mg./100 c.c. potassium	
Maximum increase			5.9 mg./100 c.c. potassium	

*1st spec. lost.

within three minutes after restoration of the circulation. The smallness of the rise in serum potassium in relation to the profound events initiated by it needs no more comment than a statement that its increase in the blood does not necessarily mirror the content of the tissue cells and intercellular fluid, inasmuch as animal experimentation by Noonan, et al.,²¹ has shown a temporary lack of equilibrium between the potassium in these locations and the blood proper.

Contrasted with this increase in the potassium ion during ischemic work is the fact that it remains normal after almost double the same amount of work when the latter is done with an intact circulation.

TABLE IV

CASE	REST (CIRC. NORMAL)	WORK (CIRC. NORMAL)
39B—GR	15.4	15.7
39C—KH	16.9	17.4
39D—MS	21.6	21.2

Superficially, these results seem to belie the studies of Fenn and Cobb,²² which show an increase in potassium after muscular contraction and stimulation. One must not forget, however, that these figures were obtained on animals, and that the period of stimulation lasted as long as a half-hour or more before a significant increase was obtained. Our

experiments on human beings were closer to being physiologic. We were unable to demonstrate a rise in potassium during exercise with a normal circulation, although we do not doubt such an increase exists. It must, however, be fleeting. The situation is modified by slowing or halting blood flow, for, in this way, potassium accumulates instead of being promptly washed away.

In order to exclude any influence of circulatory arrest alone on the potassium level, in several experiments we occluded the circulation to one arm for 2½ minutes. This was perhaps a minute longer than the usual period of exercise during ischemia. Nevertheless, there was no effect on the potassium level.

TABLE V

CASE	CONTROL	AFTER 2-3 MINUTES
	CIRC. NORMAL	CIRC. OCCLUDED
40A-KH	17.0	17.2
40B-ID8	19.2	18.7
40C-MG	20.0	19.2

To obviate any possibility that blood concentration in the ischemic region might possibly alter the potassium level, hematocrit readings were made (Table VI). They showed that hemoconcentration did not occur.

TABLE VI

CASE	REST, WITH CIRC. NORMAL		AFTER ISCHEMIC WORK	
	R.B.C. (%)	PLASMA (%)	R.B.C. (%)	PLASMA (%)
55A Tr	47	53	47	53
55B Bo	44	56	45	55
55C St	51	49	52	48

Heating the ischemic forearm has been shown to cause a characteristic aching pain like that produced by exercise during ischemia, but not as intense or as rapid in onset. These differences² we attributed to the varying amounts of time required for the muscles to be heated through the insulating barrier of skin and subcutaneous tissue, and the marked difference in the effect on tissue metabolism of the two methods; exercise undoubtedly has a much greater effect. The effect of heating on the potassium level in the ischemic arm, although not constant and not too impressive, is interesting, and favors the contention that it might be increased tissue metabolism rather than any definite metabolic phase of muscle contraction which liberates the potassium ion.

II. INTRAVASCULAR INJECTIONS

A great many substances have been introduced into the human body in attempts to influence the development of pain, e.g., the ingestion of acid or basic substances to change the pH (Katz, et al.²), the percutaneous injection or application of histamine (Rosenthal and Minard¹⁰), the subcutaneous and intramuscular injections of various ions by

TABLE VII

CASE	REST CIRC. NORMAL	OCCCLUSION AND HEATING AT 115° F.	RECOVERY 3 MIN. AFTER RELEASE	REMARKS
49B KH	19.2 mg. % K	22.0 mg. % K	18.8 mg. % K	Increase in K
49C GR	17.1 mg. % K	20.2 mg. % K	16.7 mg. % K	Increase in K
50A IW	19.4 mg. % K	19.4 mg. % K	20.7 mg. % K	No increase with heating
50B AS*	18.7 mg. % K	18.9 mg. % K	18.7 mg. % K	No increase with heating
51A KH	17.8 mg. % K	20.7 mg. % K	17.8 mg. % K	Increase in K

*Only mild pain experienced after 15 minutes' immersion in water bath at 115°. This subject was able to make 100 ischemic contractions of his arm before severe pain was experienced. Possibly insufficient heating explains the result in this case.

Maison,¹⁴ and the intravascular introduction of extremely irritating solutions²³ which were so painful that frequently general anesthesia had to be employed to lessen the effect.

Our objections to most of this work have been two: (1) the quantities introduced far exceeded physiologic limits, and (2) the route of injection

TABLE VIII

	CASE	SUBSTANCE	VESSEL	RESULT
(A) VASODILATING SUBSTANCES	35B	Papaverine $\frac{1}{2}$ gr.	A. Fem.	Hyperemia of limb
	36D	Papaverine $\frac{1}{2}$ gr.	A. Fem.	Hyperemia of limb
	36G	Mecholyl 100 gamma	A. Fem.	Hyperemia, goose-flesh, sweating of limb
	35C	Histamine 50 gamma	A. Fem.	Hyperemia of limb
	35D	Histamine 50 gamma	V. Fem.	Flushing of face
	36C	Histamine 60 gamma	A. Fem.	Hyperemia of limb
	36B	Histamine 75 gamma	A. Fem.	Hyperemia of limb
(B) POTASSIUM CHLORIDE (1% SOLUTION)	41A	KCl 5-10 mg.	A. Fem.	No ardent reaction (insuff. amt.)
	41B	KCl 20 mg.	A. Fem.	No ardent reaction (insuff. amt.)
	48B	KCl 10 mg.	A. Brach.	No ardent reaction (insuff. amt.)
	49A	KCl 20 mg.	A. Brach.	No ardent reaction (insuff. amt.)
	48A	KCl 30 mg.	A. Brach.	Agonizing pain persisting for 20 min. and disappearing gradually.
	52C	KCl 30 mg.	A. Brach.	Very severe pain and slight vasodilatation. Effects persisted for $\frac{3}{4}$ hr.
	54A	KCl 30 mg.	A. Brach.	Very severe pain and slight vasodilatation which persisted for 15 min.
	54B	KCl 30 mg.	A. Brach.	Very severe pain persisting for 10-15 minutes and accompanied by slight vasodilatation
	56A	KCl 70 mg.	Antecub. V.	Control—no effect
	56B	KCl 100 mg.	Antecub. V.	Control—no effect

tion and the irritating nature of the solutions themselves precluded any possibility that the conclusions drawn could be reliable.

Although the injection of suspected substances intra-arterially in the attempt to reproduce the pain of muscular ischemia is, at best, a crude physiologic method, it was nevertheless done with varying amounts of vasodilating substances and an isotonic solution of potassium chloride (Table VIII).

Substances such as histamine, papaverine, and mechohyl, with their known dilating effect on vessels in muscular tissue, do not produce pain upon intra-arterial injection, which is the most reliable and direct method of placing these metabolites in the vicinity of the muscle cells.

Potassium, on the other hand, when introduced in sufficient amount, produces such severe pain that it could be tried on but few subjects. The pain started a few seconds after injection and spread distally to the hand and fingers in the next 20 to 30 seconds. Our subjects, after they recovered sufficiently to be able to talk, called it the most severe pain they had ever experienced, and described it as "aching," "like a cramp," "sharp and hard," etc. The pain rapidly reached its acme and continued to be most severe for ten to twenty minutes. A mild, but definite, hyperemia of the skin was present throughout this period. The muscle power was markedly impaired; the subjects volunteered the information that the arm was "weak and they couldn't move it well." After the intense pain had diminished, muscle soreness distal to the point of injection in the forearm invariably occurred. This lasted as long as $\frac{3}{4}$ hour or more.

DISCUSSION

The potassium ion, which is preponderantly intracellular, plays an important role in tissue metabolism. Muscle cells are especially rich in potassium. Baetjer²⁴ showed that, if the blood flow to the hind limb of the cat was reduced by mechanical occlusion or by vasoconstriction from sympathetic stimulation, the amount of potassium in samples from the femoral vein was suddenly augmented by 60 per cent or more when the rate of blood flow had been reduced to 20 per cent of its normal value. This was thought to be caused by liberation of potassium from the muscle fibers as a result of asphyxia, not by concentration of blood or diffusion of potassium from the erythrocytes into the plasma. Since then, independent investigations have shown that any asphyxial state, not only local vascular occlusion, may produce the same increase in potassium. It must be emphasized again that these studies were carried out on animals, and under conditions far removed from those of our experiments. The time factor, mode of occlusion, and other conditions were not analogous to those of our experiments on human beings. For example, we found no increase in potassium after circulatory arrest of two to three minutes. We do not mean to imply that this might not

occur in more extreme conditions comparable to those in the animal experiments.

Fenn and his co-workers have clearly demonstrated that in electrically stimulated muscles of various experimental animals there is a loss of potassium in exchange for sodium and a gain of water. A further contribution was the evidence that, after voluntary contraction, the same diminution of potassium in muscle and a corresponding increase in the amount liberated to the blood plasma occurred; the loss of potassium was proportional to the amount of work done. This increase of potassium started simultaneously with the onset of muscle stimulation and contraction, and the amount returned to normal in the blood stream within five minutes after the stimulation had ceased.

Other bits of experimental evidence seem to fit into this composite picture which we have been presenting. Katz and Katz,²⁵ as well as Feldberg and Guimaraes,²⁵ have pointed out that the intra-arterial injection of potassium results in the liberation of adrenalin from the adrenal glands. Dawes²⁶ has further shown that potassium chloride not only causes vasodilatation in probable muscle, but also a general rise in blood pressure due to the release of adrenalin.

Potassium enters into all of these intricate and closely bound relationships—asphyxial states, blood pressure rise, vasodilatation, secretion of adrenalin, etc. It is the only constituent of the tissues which fits our criteria for the P substance; it is a normal tissue metabolite found in great concentration in the muscle cells. It is released from the muscle during exercise and in anoxemic states. During ischemic exercise of one to one and one-half minutes' duration it is liberated simultaneously with the development of pain, and accumulates sufficiently to appear in increased concentration in the blood stream. It is capable of rapid dispersion as soon as the circulation is restored, and returns to its normal level within three to five minutes thereafter. Finally, potassium is the one substance which, when injected intra-arterially in isotonic solution and in amounts which might ordinarily be released physiologically from a corresponding mass of contracting muscle,²⁷ produces such severe pain that we could try it on but a few subjects. This pain is, in many respects, like the severe aching sensation complained of after ischemic work, but intensified and magnified. It is not due to irritation of the arterial wall because there is a latent period of several seconds before pain begins, implying penetration to more distal regions, and because the amount required depends on the mass of tissue affected. Thus, the amounts which produced severe pain in the arm had absolutely no effect on the leg. The intravenous injection of double or triple the amounts used for intra-arterial injection was absolutely innocuous and produced no symptoms. The difference must be explained by dilution, in the latter instance, by the blood before it reaches the end organs in the muscles; in the former it is transferred by the most physiologic and direct route to the muscle cells.

One cannot say from this evidence that potassium is the P factor itself, but only that it is intimately bound up with the phenomena of pain in the ischemic state in some way that is not yet clear. Although our own injection experiments seem to show a direct effect of the potassium ion on the nerve endings in the tissues, one cannot exclude the possibility that some reflex or even physicochemical change initiated by the release of potassium might be a factor. It may well be asked why there is no apparent effect on pain production in diseases such as periodic familial paralysis and Addison's disease, in which profound alterations in potassium levels, even greater than those we have found, are known to occur. In explanation of this, we wish to stress once more that the level in the blood does not necessarily mirror the changes taking place in the tissues, and that, in so far as pain sensation is concerned, it may be the sudden change in potassium concentration around the sensory receptors during ischemic contraction which is involved.

SUMMARY

It is suggested that potassium plays a major role in the genesis of ischemic pain; this hypothesis is based partly on experimental work on animals, and, to some extent, on the clinical observations and biochemical studies we have presented.

During muscular activity potassium is liberated from the cells. Under ischemic conditions, a physical factor is introduced which leads to a rapid accumulation of the potassium ion until it reaches the threshold required for stimulating the pain end organs in the muscle.

It is further assumed that an increase in the activity of tissues other than muscle, possibly skin, might also result in discharge of potassium, and, under suitable ischemic conditions, result in pain.

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THE RELATIONSHIP OF CONGENITAL HEART DISEASE TO PREMATURE BIRTH

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IN ORDER to elucidate the possibility of a direct or mutual relationship between prematurity of birth and congenital cardiovascular defects, or of a common dependence on some abnormality of germ plasm or fetal life, we have carried out a twofold study. First, in order to learn whether prematurity is a factor that may favor the development of congenital heart disease, we have examined, with the kind permission of the staff, the autopsy protocols of prematurely born babies at the Boston Lying-In Hospital, and have ascertained the incidence of such maldevelopment. Second, we have found out how often prematurity of birth occurred among patients with congenital heart disease who attended the Out-Patient Departments of the Massachusetts General Hospital, Children's Hospital, and Boston Lying-In Hospital. We have ascertained, in almost all these cases, the birth weight, and have assembled a special group of patients who weighed less than 2,500 grams (5.5 pounds) at birth, in accordance with the criteria proposed by Ylppö.¹ This author made a common group of all babies who weigh less than 2,500 grams because they are incompletely developed, in poor condition for an independent life, and have some characteristic stigmata. Most of the babies of this group are born prematurely, but they may be born at full term or even past term. Thus, Capper² found that, in fifty-six of 437 cases in which the infants weighed less than 2,500 grams, the duration of the pregnancy was not known; 276, or over 72 per cent, were born prematurely, 103, or 27 per cent, were born at full term, and two were past term (these two weighed 1,800 and 2,300 grams, respectively, at birth). That is why some American authors designate as "immature infants" those that weigh less than 2,500 grams, and call "premature infants" those who are born before term, that is, before the 270th day of the pregnancy. At the Boston Lying-In Hospital it has been the custom to call infants that weigh less than 5 pounds (2,268 grams) premature, and below 5½ pounds (2,495 grams), immature. The criterion of the weight not only has clinical significance, but is useful also because, as we have observed many times, it is impossible to know the exact duration of the pregnancy, and because statistics about prematurity are based largely upon the birth weight. Body length would probably be the best criterion of all, but it is not routinely recorded and is often difficult to measure in the first place.

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A. AUTOPSIES ON PREMATURELY BORN BABIES

The records of 139 autopsies on prematurely born babies were examined; the birth weight of 129 of them was less than 2,500 grams. The duration of life after birth had been, in most instances, only a few hours; the longest period of life was eight days. Of all the 129 infants who weighed less than 2,500 grams at birth, the weight of the heart was more than 17 Gm. in only eleven; this is the average normal heart weight of a full term baby. The weights of the sixteen hearts in the whole group of 139 that weighed more than 17 grams were 30, 27, 27, 22, 20, 20, 20, 19, 19, 19, 19, 19, 18, 18, 18, and 18 grams, respectively. In no case was closure of either the foramen ovale or the ductus arteriosus recorded.

There were only three cases of malformation of the heart among the 139 premature infants (2.2 per cent); these were as follows:

CASE 1.—Interventricular septal defect, 7 mm. in diameter, behind the left lateral leaflet of the tricuspid valve. The weight of the heart was 20 grams.

CASE 2.—Multiple congenital malformations of the lungs, heart, and intestine. The right auriculoventricular valve had only two cusps. The pulmonary veins emptied into the superior vena cava, at approximately 7 mm. from the opening of this vessel into the right atrium. The fossa ovalis measured 1 cm. in diameter, and was only partly closed by a veil-like septum which left patent approximately half of the foramen. The pulmonary artery was normal. At a point 4 mm. from the free edge of the posterior cusp of the pulmonary valve, a small opening, measuring no more than 1 mm. in diameter, was found. This opening continued into a small artery which passed upward and entered the left lung, where it divided into several smaller branches which supplied both left and right lungs. Immediately above this opening the ductus arteriosus began; it was 1.1 cm. in circumference and 1.2 cm. long. The left atrium was of approximately normal size, but no blood vessels coming from the lungs were found entering it. Immediately below the foramen ovale, in the left atrium, there was a small opening which measured about 1 mm. A probe inserted into this opening passed between the trabeculae of the right atrium.

CASE 3.—Anomaly of the vessels of the aortic arch: the right and left common carotid arteries arose together to form a short common trunk as the first branch of the aortic arch. The second branch was the left subclavian. The third was the right subclavian, which left the aortic arch posteriorly and passed behind the trachea to reach the right side.

The infant whose heart weighed 30 grams had, in addition, hepatomegaly, renomegaly, and splenomegaly.

If we consider the 129 infants who weighed less than 2,500 grams, the incidence of congenital malformation of the heart was three cases, or 2.3 per cent. Including all the 139 cases, the incidence was still only three cases, or 2.1 per cent.

B. PATIENTS WITH CONGENITAL HEART DISEASE

We have examined the histories of a large group of patients with congenital heart disease, and looked for the birth weight and evidence

of prematurity, and have sent letters asking for this information in the cases in which it was not recorded. We have obtained such data on 188 patients. These we have divided into two groups:

1. Patients whose birth weight was known. There were 148 of these. Seventeen of them, or 11.4 per cent, weighed less than 2,500 grams.

2. Patients concerning whom it was specified whether or not birth was premature. There were 172 of these, of whom seventeen, or 9.8 per cent, were born prematurely.

In the whole group of 188 patients there were twenty-one with patency of the ductus arteriosus, all of whom were born at full term. In nineteen of the twenty-one the birth weight was recorded as being less than 2,500 grams in only one case, that is, 5.2 per cent. Patency of the ductus is, of course, actually a postnatal development, although its potentiality may rightly be considered congenital. There were four patients with an interauricular septal defect, all of whom were also born at full term. Among the thirteen cases of the tetralogy of Fallot seen at the Children's Hospital, there were only two premature births.

DISCUSSION

A priori, we may suppose that there are two critical periods in the development of the heart with regard to congenital malformation: the first between the fifth and eighth weeks, at which time the involution of the bulbus and the formation of the septa take place, and the second after birth, when the ductus arteriosus and the foramen ovale close.

Patten³ has demonstrated that the foramen ovale is normally open at birth, when it is possible to pass a probe through it, although functionally it should be considered closed. He considers three periods in the closure of the foramen ovale. The first covers the first month after birth, during which a probe can be passed freely. The second period lasts six to eight months, when the foramen ovale is reduced to a slit and the movable valve is converted into a fixed septal structure; passage of a probe is still possible, but more difficult. Finally, during the last period the valve of the foramen ovale adheres to, and becomes a part of, the interauricular septum. Patten considers incomplete adhesion of the valve, with patency to a probe, as a variation of the normal, because it is found in 25 per cent of normal adult hearts.

Christie⁴ studied 590 normal hearts of children who were between one day and one year old, and found that closure of the foramen ovale occurred before the twelfth week after birth in 87 per cent of the cases. Closure of the ductus arteriosus took place before the eighth week after birth in 88 per cent of these cases.

Ylppö¹ studied the closure of the ductus arteriosus in immature children, and found that, in most of them, one or two weeks after birth, the ductus arteriosus was no longer permeable by the blood coming from the aorta.

Some authors have supposed that prematurity of birth would tend to favor persistence of the ductus arteriosus or of the foramen ovale. Hess, Mohr, and Bartelme⁵ found, in 385 autopsies on premature infants, twelve cases of definite cardiac malformations, that is, 3.1 per cent (including five cases of ventricular septal defect, the commonest of the anomalies). This percentage is about the same as that which we found in autopsies on premature babies.

Dioxades⁶ thinks that prematurity should favor the persistence of certain characteristics of the fetal heart, namely, the relatively small left ventricle and relatively big left auricle, the relatively big right ventricle and relatively small right auricle, and persistence of the foramen ovale.

In Capper's series² of 437 premature infants who were followed to the age of 14.5 years, there were ten patients, or 2.3 per cent, with congenital heart disease, seven of which were autopsied; the other three were alive, and the type of their lesions was not specified. The post-mortem diagnoses in the seven autopsy cases were: simple foramen ovale in one, foramen ovale and patent ductus arteriosus in three, aneurysm of the ductus arteriosus in one, pulmonary stenosis in one, and dextrocardia with pulmonary stenosis in one.

As we have said, the incidence of prematurely born children in our series of cases of congenital heart disease was 11.4 per cent, considering only those who weighed less than 2,500 grams. What is the general incidence of premature and immature births? It varies a great deal with statistics. Ylppö¹ states that the figure is 5 per cent in Moscow (there were 6,036 children with a birth weight of less than 2,500 grams out of 121,626 deliveries). Pinard, Hahn, and François (cited by Ylppö¹) found 29,071 "premature" infants (babies with a birth weight of less than 2,500 grams) out of 188,204 births in France, which is 15.4 per cent. Ylppö¹ calculates that in Germany the incidence of immaturity is over 10 per cent. Schultze⁷ found 6.6 per cent immaturity among 10,355 new-born children. American statistics give lower figures. Einhorn⁸ found 204 immatures that weighed less than 2,500 grams among 12,335 infants born in Albany, that is, 3.47 per cent. Wilcox⁹ found 330 children that weighed less than 2,500 grams among 10,163, that is, 3.24 per cent. Hess¹⁰ reported an incidence of 3.77 per cent among 49,425 infants. At the Boston Lying-In Hospital, information based on 27,713 births from 1933 through 1940 shows an incidence of premature births (1- to 5-pound infants) which varies annually from 2.9 to 3.5 per cent, and, of immature infants (below 5½ pounds), that varies from 4.5 to 5.5 per cent. Since our analysis should be compared with these various American figures, it does appear that at least twice as many of our patients with congenital heart disease were premature as in a control series of the population at large.

SUMMARY AND CONCLUSIONS

1. Among 139 autopsies on prematurely born children we found only three cases (2.2 per cent) of congenital malformation of the heart.

2. Among 148 patients with congenital heart disease whose birth weight was known, we found seventeen who weighed less than 2,500 grams at birth, that is, 11.4 per cent. Among 172 cases in which the duration of pregnancy was ascertained, there were seventeen patients who were born prematurely, that is, 9.8 per cent.

3. The incidence of prematurity of birth in our cases of congenital heart disease was about twice that in deliveries of infants with normal hearts. Nevertheless, it happened that only one of nineteen patients with patency of the ductus arteriosus (in reality a postnatal development) of this series weighed less than 2,500 grams at birth, all four patients with auricular septal defects were born at full term, and only two of thirteen patients with the tetralogy of Fallot were premature.

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HISTOLOGIC DEMONSTRATION OF ACCESSORY MUSCULAR CONNECTIONS BETWEEN AURICLE AND VENTRICLE IN A CASE OF SHORT P-R INTERVAL AND PROLONGED QRS COMPLEX

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THERE has been much speculation concerning the mechanism responsible for the electrocardiographic anomaly of an abnormally short P-R interval in association with a prolonged QRS complex. That it may occur in presumably undamaged hearts is strongly suggested not only by the pioneer study of Wolff, Parkinson, and White,¹ but by subsequent reports, as well. Recently, Hunter, Papp, and Parkinson² have listed the various hypotheses which reflect the efforts made to account for the phenomenon.

The hypothesis of an accessory pathway of A-V conduction was first suggested as a possible explanation by Holzman and Scherf,³ in 1932. The same hypothesis was advanced independently by two of us, and subjected to analysis in the light of what was then known about the subject, in a paper⁴ which was in press at the time Holzman and Scherf's article appeared. It has continued to seem to us to be the only explanation thus far proposed for this phenomenon⁵ which offers no violence either to mathematical probability or to generally accepted views regarding the spread of the excitatory process. Moreover, the recently reported ingenious experiments of Butterworth and Poindexter⁶ show that similar electrocardiograms, with a short P-R interval and prolonged QRS complex, can be produced in animals by the introduction of an artificial, accessory pathway.

So far as we are aware, no one has yet presented histologic proof of the existence of accessory muscular connections between the auricles and ventricles of a patient with this type of electrocardiographic abnormality. The present paper furnishes this proof.

CASE REPORT

A. F., a 13-year-old boy, was admitted to the Allentown State Hospital for the Insane on April 30, 1935. He was under the care of Dr. A. Lindenfeld, to whom we are indebted for much of this information. Examination on admission showed no evidence of cardiovascular disease; the heart was not enlarged; the rate was 74 per minute; there were no auscultatory abnormalities; and no history suggesting heart disease or reduced exercise tolerance was obtained. His diagnosis was "Behavior problem with borderline intelligence."

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On October 18, 1936, while playing football, he had his first known attack of paroxysmal tachycardia. The cardiac rate was 180 per minute and the rhythm was regular. He was cold, clammy, and dyspneic, and had pain in the right upper quadrant of the abdomen. He was given an injection of morphine. After about an hour, he coughed up a small amount of bloody sputum, and the attack terminated. The next day premature beats were noted. One of us (G. D. G.) saw him after this attack and could elicit no evidence of cardiovascular disease. Thereafter his heart was studied repeatedly by physical examination and by special methods. A tele-roentgenogram showed that it was normal in size and shape; the transverse diameter was 12.5 cm., with a chest diameter of 27 cm. The electrocardiogram showed a short P-R interval, a prolonged QRS complex, and abnormal T waves (Fig. 1). Since he was powerfully built and athletic in type, with no demonstrable abnormality except that in his electrocardiogram, his activities were not restricted. In December, 1937, he was said to be playing basketball, without cardiac symptoms.

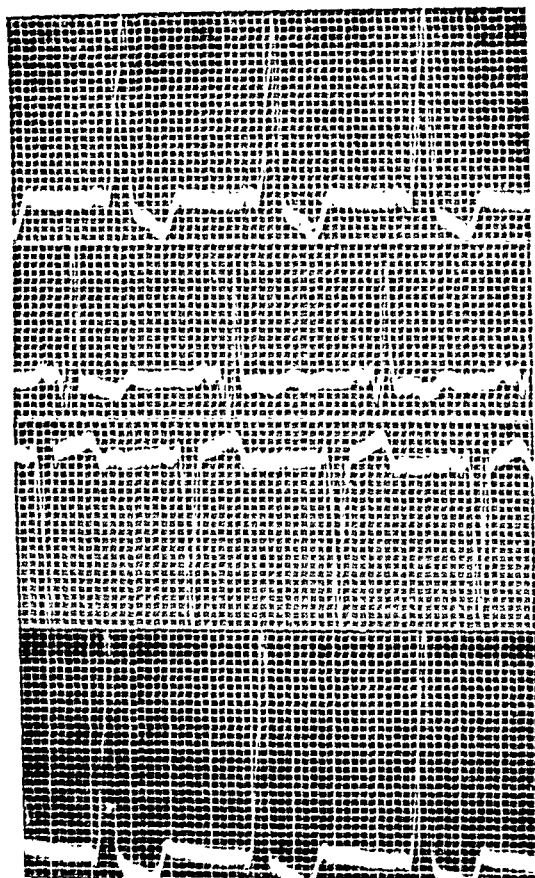


Fig. 1.—Electrocardiogram of A. F., taken May 12, 1938, showing the short P-R interval and prolonged QRS complex.

On March 27, 1938, a routine physical examination showed nothing new. On March 31, 1938, after riding on a merry-go-round, he experienced dizziness, palpitation, severe substernal distress, and shock. He was in a cold sweat, and seemed very ill. The heart rate was "over 150." He was helped back to the dormitory. Carotid sinus pressure was ineffective. After seven hours, the paroxysm of tachycardia ceased spontaneously.

On April 28, 1938, one of us (G. D. G.) examined him again. A somewhat accentuated second sound was heard at the base of the heart. Exercise was followed

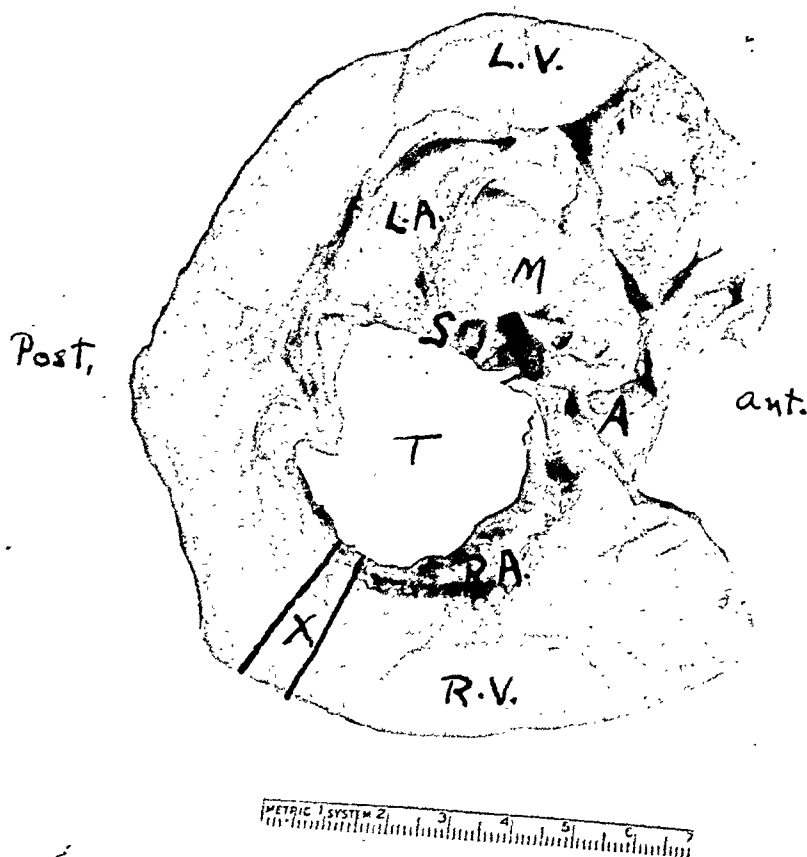


Fig. 2.—A portion of the heart of A. F. to show the manner in which it was prepared for serial section, and to indicate the location of the accessory muscular connections between auricle and ventricle, which are shown in Figs. 3 and 4. The ventricular tissue 2 cm. below, and the auricular tissue 1 cm. above, the auriculoventricular groove were cut away. The remaining part of the heart was placed on a flat surface, with the ventricles against that surface, and photographed from above. Thus one is looking down on the auricular part of the preparation, with the anterior part of the heart to the right; the right auricle (RA) and the right ventricle (RV) are below; the posterior part of the heart is to the left; the left auricle (LA) and left ventricle (LV) are above. S is the septum, A is the aorta, M is the mitral valve, and T is the tricuspid orifice. X indicates the region in which the muscular connections between the right auricle and right ventricle, shown in Figs. 3 and 4, were found.

Fig. 3.—Photomicrographs of sections taken through the auriculoventricular groove at position X (Fig. 2), showing the first muscular connection that was found between the right auricle and ventricle. All sections were stained with Masson stain, which colors the muscle red and the connective tissue green. Photographed in black and white, using a green filter, the contrast is fairly definite, but not so sharp as in actual sections. It is much more convincing to follow these muscular connections by looking at each successive slide. However, this figure is an attempt to demonstrate in a few key photographs the appearance of the first muscular connection which we encountered. In the photographs the muscle is dark and the connective tissue light. Magnification 37X. (a). (Section 1164A) The auricular muscle (A) is shown to the right, the ventricular muscle (V) to the left, and the ventricular cavity (VC) below, with a "bay" above a projection (P). Beginning near the right upper corner of the picture, a bridge of muscle (B) is seen extending down and to the left, and curving back toward the right again, just beneath the endocardium. Just to the left of this structure, across the bay and jutting into the ventricular cavity, is a portion of the ventricular muscle (M) which in subsequent sections will be seen to unite with the muscle in the bridge (B) and then rejoin the main ventricular muscle. (b). (Section 1171A) The auricular muscle (A) is shown above and to the right, the ventricular muscle (V) below and to the left, and the ventricular cavity (VC) below, with a "bay" above the projection (P). Across the upper part of this "bay" the bridge of muscle (B) is beginning to pass. This muscle tissue now is separated from the auricular muscle by fibrous tissue, and is projecting out into the "bay." Continuous with the ventricular muscle (M) which, in section 1164A, was jutting out into the "bay," is the island (M), now lying free in the "bay," just to the left of B. (c). (Section 1172A) The general relationships of auricular muscle, ventricular muscle, and ventricular cavity are much like those in section 1171A. The bridge of muscle (B) has projected much further out into the bay, and has almost become an "island," just to the right of the island (M) described in Fig. 3b. (d). (Section 1180A) The bridge of muscle (B) now lies free as an "island" in the "bay" just to the right of the island (M). (e). (Section 1189A) The bridge of muscle (B) has united with the island (M) and is continuous with the ventricular muscle, but the muscle of the two

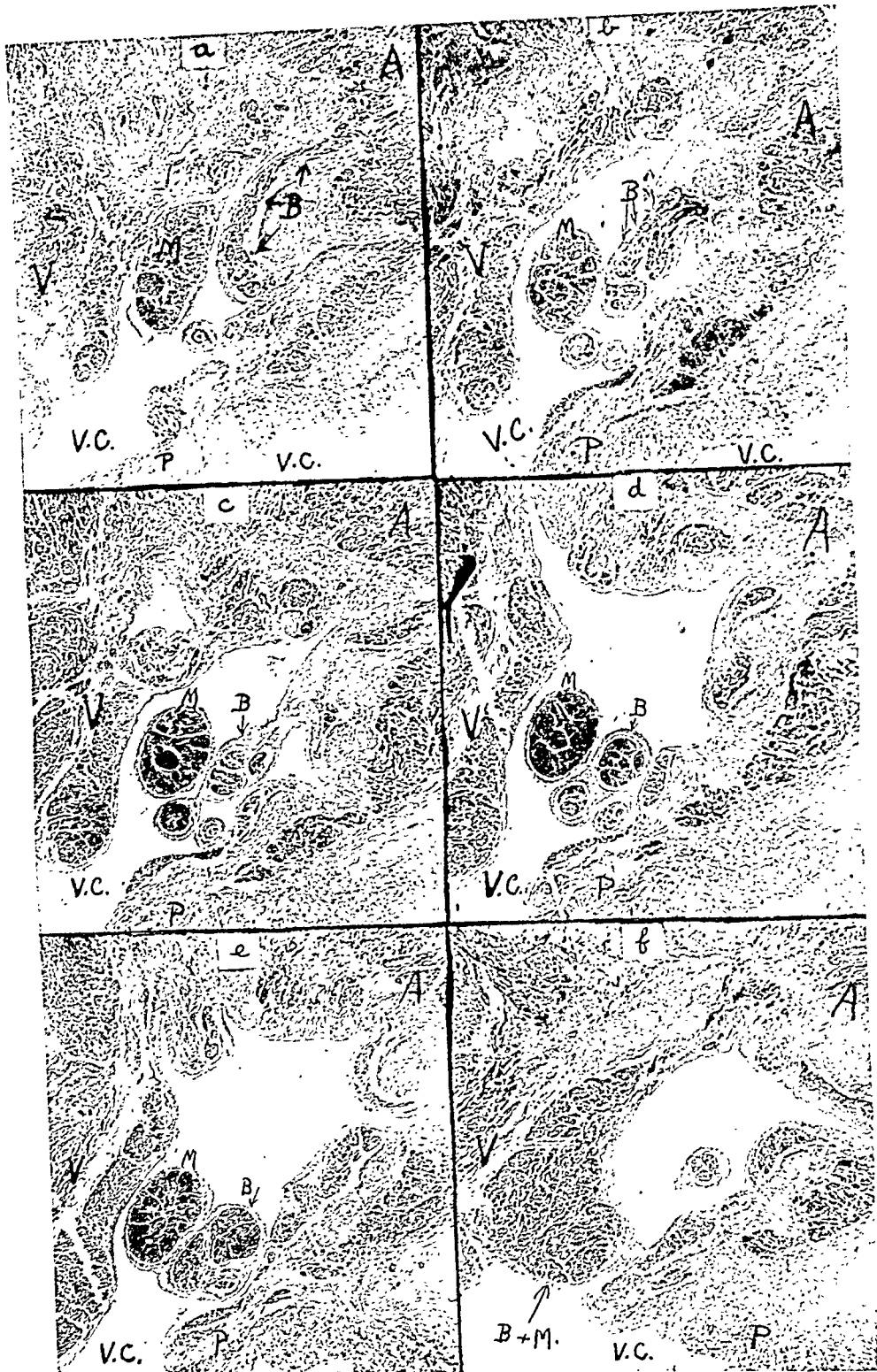


Fig. 3.

structures is still separated by fibrous tissue. (f). (Section 1207A) Fibrous tissue no longer separates the components of the "island," derived from auricle and ventricle, as it did in Section 1189A. Moreover, the island B + M is now seen uniting with the ventricular muscle. Subsequent sections (not shown in this figure) demonstrated that this muscular mass communicated freely with the main mass of ventricular muscle.

Thus this first series of figures shows the first muscular connection which was found. It connects the auricular to the ventricular muscle by forming a bridge over a "bay" in the ventricular cavity. There is no "nodal tissue" in this muscle bridge, such as was described by Kent.

by premature beats. Otherwise, no abnormalities were found on physical examination. On May 12, 1938, electrocardiograms were taken after exercise and after atropine sulfate administration (gr. $\frac{1}{100}$ by hypodermic). No definite changes resulted from these procedures. The P-R interval and QRS complexes continued to show the anomaly.

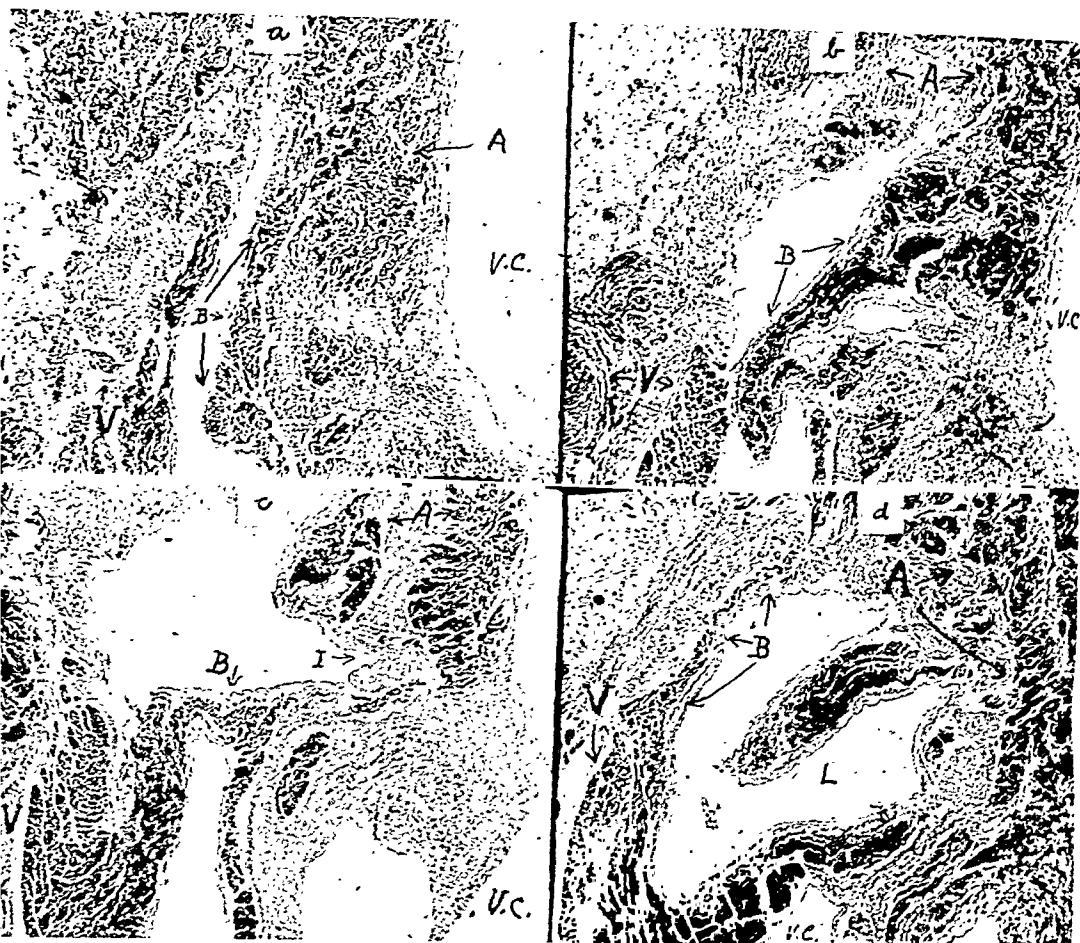


Fig. 4.—A series of four photomicrographs showing the second muscular connection in *a*, *b*, and *c*, and the third muscular connection in *d*. The stain and photography were the same as described for Fig. 3. (*a*). (Section 1230B) The auricular origin of the second muscular connection (*B*) is shown. The ventricular cavity (*V.C.*) lies to the right. In the middle of the picture is a long narrow "bay" which is part of the ventricular cavity, and which connects with it below and to the right, beyond the limits of this picture. The auricular muscle (*A*) lies above. Extending down from it, along the right side of the "bay," is the beginning of the second muscular connection (*B*). The ventricular muscle (*V*) lies along the left shore of the "bay." (*b*). (Section 1249C) The second muscular connection (*B*) projects across the "bay" and begins to join the "shore" on the left side of the "bay," where the ventricular muscle is situated. As in the preceding section the auricular muscle (*A*) is above and to the right, and the ventricular muscle (*V*) below and to the left. The bay, which is being traversed by the muscular bridge (*B*), is a part of the ventricular cavity. (*c*). (Section 1255B) The second muscular bridge (*B*) passes across the "bay" and joins the ventricular muscle (*V*) which lies along the left side of the "bay." The bridge (*B*) now shows no muscular connection with the auricular muscle (*A*), which lies above and to the right; it is separated by the indentation (*I*) of the "shore of the bay." (*d*). (Section 1269B) The third muscular connection. The auricular muscle (*A*) lies at the top and along the right margin of the picture. The ventricular muscle (*V*) lies below and to the left. A large "lake" (*L*) lies in the center. The third muscular connection (*B*) is the tenuous strand of muscle extending along to the left shore of the "lake." This is the most delicate of the three muscular bridges. It is the only one which may be seen in its entirety in one section, and it is the only one which does not cross the ventricular cavity.

The remains of the second muscular connection which made a "lake" of the upper portion of the "bay" (of Fig. 4*b* and *c*) is seen along the lower margin of the "lake," in Fig. 4*d*, lying in the strip of tissue separating the ventricular cavity (*V.C.*) from the "lake."

On May 17, 1938, while wrestling with one of his friends (not really fighting), he was seized with palpitation and severe substernal distress. The heart rate was "over 150." An hour later he said he felt better. Two hours after the onset he died suddenly after drinking a glass of water.

Examination of the heart after death disclosed no gross evidence of disease. The organ was not enlarged. The valves and coronary vessels were normal. Nothing was found elsewhere in the body to account for the sudden death.

Histologic Studies.—It was decided to make serial sections around the auriculo-ventricular groove in an attempt to discover whether or not any evidence could be obtained concerning the hypothesis of an accessory pathway of auriculoventricular conduction,³⁻⁵ i.e., whether there was a muscular connection between auricles and ventricles in addition to the main auriculoventricular bundle. In order to do this, the ventricles were cut off 2 cm. below the auriculoventricular groove, and the auricles were cut off 1 cm. above the groove, as shown in Fig. 2. Blocks of tissue were cut sagittally, beginning just to the right of the aorta. The sectioning was carried around toward the right from that point. Every fifth section was stained and studied.

In section 1161 a muscle bundle was seen leaving the auricular muscle. It joined the ventricular muscle in section 1207, after passing by means of a bridge of tissue across the ventricular cavity just below the attachment of the tricuspid valve. Consequently, every section, instead of every fifth section, was stained from 1158 to 1306, so that there were sections A, B, C, D, and E for each of these numbers. Thus a total of 2897 stained sections was studied.

Figs. 3 and 4 represent an attempt to show the accessory bridges of muscle tissue which were found between the right auricle and right ventricle. Three such connections were found in the general position of the letter X in Fig. 2, at approximately the right lateral border of the heart. Although it might have been interesting to carry the sections completely around the auriculoventricular groove, it was decided to stop when these definite muscular connections were discovered because it seemed that the information desired had already been obtained; namely, that, in the heart of a patient who had had a short P-R interval and an aberrant QRS complex, there were definite muscular connections between auricle and ventricle, bridging the auriculoventricular groove, of a type which should be able to conduct an impulse from auricle to ventricle.

DISCUSSION

At the end of the last century, A. F. Stanley Kent⁷ became interested in the problem of the conduction of impulses from auricle to ventricle. He made extensive microscopic studies of the auriculoventricular groove, and published his first observations in 1893,^{7a, 7b} describing the auriculoventricular muscular connections which he found in various mammals at different stages of development. He demonstrated by his studies on animals^{7a} that young rats and rabbits have a very rich muscular anastomosis between auricle and ventricle. As the age of the animal increases, or as the animal scale is ascended, these muscular connections become fewer in number. The monkey exhibits the fewest auriculoventricular muscular connections, but does have them. (Kent was the first to describe the auriculoventricular bundle, although His' name has been applied to it.)

After these early publications, there was an interval of twenty years before Kent's next papers appeared. In these^{7c-7i} his main interest

shifted from the lower animals to man, and he dealt primarily with an auriculoventricular connection which lay at the right border of the heart and connected the right auricle and right ventricle; he called it the "right lateral bundle." He showed a number of photomicrographs of this structure.^{7c, 7e, 7g, 7i} It is a very definite muscular bridge between auricle and ventricle. Usually the auricular muscle enters a mass of "nodal tissue" in the auriculoventricular groove, "interposed in the course of the muscular path between auricle and ventricle." However, one of his early photomicrographs fails to show "nodal tissue."^{7c} The implication of Kent's statements is that this right lateral bundle was found in all of the human hearts which he studied. However, he did not actually make this statement. He mentioned several experiments performed by himself⁷ⁱ and others^{7h} which demonstrated to his satisfaction that, in animals, this structure was capable of conducting impulses from auricle to ventricle after the main bundle had been cut. He also referred to observations^{7h} which made him feel that the right lateral bundle may function in man in certain cases. However, despite Kent's convincing photomicrographs, interest in the "right lateral bundle" waned, possibly as a result of Lewis' opinion,⁸ until the electrocardiographic anomaly which is the subject of this paper began to be investigated.^{3, 4}

Recently, Glomset and Glomset⁹ stated that there are "definite muscular bridges between auricles and ventricles in various places in the auriculoventricular groove," but they showed no photomicrographs and did not mention the "right lateral bundle" specifically.

The auriculoventricular connections which we are now describing had the following characteristics: (1) Three of them were located at the right lateral border of the heart. Since our study has not been extended further, it is not possible to say whether or not more such connections existed. (2) Two of the three took a rather unexpected course, in that they passed across the ventricular cavity in an actual muscular bridge. (3) No "nodal tissue" was interposed in their course, as described by Kent. Thus, these structures may not be the same as those which Kent described, although they are situated in the same general region.

These observations show that a patient with a short P-R interval and a prolonged QRS complex did have definite muscular connections between auricle and ventricle at the right lateral border of the heart. These connections were of such a nature that they should have been able to conduct an impulse from auricle to ventricle, or from ventricle to auricle.

In our first paper on this subject⁴ we attempted to account for abnormalities of the cardiac mechanism, such as paroxysmal auricular tachycardia and fibrillation, in cases of short P-R interval and prolonged QRS complex, by assuming that they are initiated by retrograde conduc-

tion, through the accessory tract, of an excitatory process which had previously been transmitted to the ventricles via the normal channels. The reports of Arana and Cossio,¹⁰ Hunter, Papp, and Parkinson,² and Levine and Beeson¹¹ indicate that there is at least some tendency toward the occurrence of paroxysmal ventricular tachycardia, as well. This could also be accounted for by a somewhat similar assumption, for, if a ventricular extrasystole forced retrograde conduction through the main auriculoventricular tract, and was followed by an aberrant auricular response, as sometimes occurs in cases in which the mechanism is otherwise normal, it might be possible, so far as the time relationships are concerned, for the impulse to be reconducted to the ventricle via an accessory conduction tract if one happened to be present. Thus premature re-entry into ventricular tissue might initiate an abnormality of the ventricular mechanism, just as premature re-entry into auricular tissue might initiate an abnormality of the auricular mechanism. These hypothetical considerations require the assumption of only one accessory pathway between auricle and ventricle. We had not previously entertained the thought that there might be more than one such pathway. The presence of multiple pathways should, it seems to us, facilitate re-entry of the excitatory process.

Thus, this study gives support to the hypothesis of an accessory pathway of auriculoventricular conduction^{3, 4} in these cases. Proof of the hypothesis, however, would require direct evidence that tracts such as we have demonstrated are capable of transmitting the excitatory process.

The patient described in this paper differed from the majority with this anomaly, in that he died in an attack of paroxysmal tachycardia, but this is the only difference. The electrocardiogram was typical, attacks of paroxysmal tachycardia are characteristic, and the patient showed no other evidence of cardiovascular disease.

If, as Kent implies, this right lateral bundle exists in all human hearts, the question suggests itself, why do not all of us have a short P-R interval and a prolonged QRS complex? We have no data upon which an answer to this question could be based.

SUMMARY

1. A patient with a short P-R interval and a prolonged QRS complex, and no other evidence of cardiovascular disease, died in an attack of paroxysmal tachycardia.
2. Gross examination of the heart showed no evidence of disease.
3. Serial histologic sections of a portion of the auriculoventricular groove showed three muscular connections at the right lateral border of the heart between the right auricle and right ventricle. Two of these bridged a small part of the ventricular cavity during their course.
4. The demonstration of the presence of these structures, which should be capable of conducting an impulse from auricle to ventricle, furnishes

further support for the hypothesis of an accessory pathway of auriculo-ventricular conduction as an explanation for this electrocardiographic anomaly.

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ACQUIRED PALMAR ERYTHEMA AND CUTANEOUS VASCULAR "SPIDERS"

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DURING the past several years, in a study of the cutaneous arterial "spiders"† which may occur in certain persons with liver disease, pregnancy, and nutritional deficiency disorders, and in apparently normal persons, observations have been made on two hundred fifty-one subjects.¹ These have been followed for periods varying from a few days to five years. Among the associated vascular phenomena, a curious hyperemia of the skin of the palms and sometimes of the soles has been encountered in a few instances.‡ This appears to have an important relation to vascular spiders. A review of the reports of similar cases has been undertaken, and personal observations on eleven new ones will be presented.

In surveying the literature one encounters great difficulty in deciding whether to include certain obscure conditions of the palms and soles among the cases here considered. Reports during the last quarter of the nineteenth century were often vague about details, so that it is difficult to make a diagnosis from the descriptions. Into the category of doubt must fall the erythrokeratosis or erythema keratodes of the soles and palms,² and related disorders.³

Erythema palmare as a distinct entity was first described in an all too brief note by Chalmers,⁴ in 1899, although this paper has not been noticed by subsequent writers. He was impressed by a remarkable palmar redness, symmetrically disposed, and most pronounced in the palmar pads of the hypothenar and thenar eminences. He found the condition only in Europeans who were residing on the Gold Coast of West Africa. There were no symptoms, and the condition was entirely innocuous, although it was apparently widely prevalent in the special group which he studied. No suggestions were put forward concerning the nature of this stigma.

In 1914, there was an interesting discussion of a case presented at a meeting of the British Dermatological Association under the title of

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†The term *vascular "spider"* was first used by Patek, Post, and Victor.¹⁸ In addition to the generic words *angioma* and *telangiectasis*, this curious arterial aneurysm of the skin has been called *spider cancer*, *naevus araneus* (spider web), *naevus arachnoideus*, *tache stellaire*, and *etoile vasculaire*. Arterial or vascular "spider," a purely descriptive name, is the simplest and most satisfactory.

‡Bizarre erythema of the palms and fingers, with or without cyanosis, has been noted in a number of conditions. Osler (Am. J. M. Sc. 152: 187, 1903) saw it in a patient with a fractured skull. A somewhat similar condition may occur in cases of the painful shoulder and hand syndrome which may follow infarction of the heart.¹ The palmar erythema to be described differs from these conditions, as may be seen in the diagrams and photographs.

erythromelalgia. Because of the absence of pain it was obviously not ordinary erythromelalgia. Parkes Weber⁵ compared the palms with those which had been noted in 1901 during an outbreak of arsenic poisoning, when the term "arsenical beer drinkers' hands" had been in vogue. It seems to have been painless. Since erythema palmare usually produces no symptoms, there should be no difficulty in distinguishing it from typical acrodynia or erythromelalgia, both of which are, by name and by definition, painful.

The next report, and the one heretofore considered as the original, was made by Lane,⁶ in 1929. He studied this phenomenon in two men who had had red palms as long as they could remember. Other members of the families had identical discoloration of the hands. Lane named the condition *Erythema Palmare Hereditarium*, and was the first to point out the hereditary and familial features. From the comments on his paper, and discussions of several subsequent reports, it became clear that many physicians had a vague familiarity with similar cases, but had given the matter no careful consideration.

After Lane's paper, sporadic notes appeared. The syndrome has occurred in association with a multitude of diseases, as shown in Table I. Among the observations which may be of significance, several stand out. Ambler⁷ was the first to record the appearance of the syndrome in a previously unaffected patient who developed liver disease. The palmar change persisted for seven years. Ambler measured the skin temperature, and found that it was considerably higher than normal. Mierowsky⁸ was the first to observe a similar erythema of the soles in a patient with the palmar change. From the description given by Parkhurst,⁹ it does not seem likely that isolated plantar erythema, with sweating and occasionally with eczema, has the same origin, but this must be settled by further study. Slight pain in the hand has been recorded only by Gottron.¹⁰ The pain was atypical, and the red areas were not similar to those of erythromelalgia, as described by Weir Mitchell, in 1872. Clubbed fingers were noted by Bloeman¹¹ in a patient who had the acquired variety of palmar erythema which had lasted 27 years. Schmidt-La Baume's¹² patient had dermatographism. He also noted accentuation of the redness of his palms after drinking alcoholic beverages. Aguilera Maruri¹³ found that the condition in a man with syphilis and tuberculosis gradually cleared up under antisyphilitic therapy, after a known duration of three years. Feldman¹⁴ was the first to point out the association with pregnancy.

Walsh and Becker¹⁵ presented a large series of cases and cited most of the antecedent reports. The thing which excited their attention was the association of palmar erythema and vascular "spiders" in pregnant women, which had never before been reported. Their detailed study included observations of the skin with a capillary microscope and histologic studies of the vascular spiders. Their paper should be con-

sulted by anyone who wishes to obtain a comprehensive grasp of the problem.

The reported cases are tabulated in Table I, along with those to be described later.

MATERIALS AND OBSERVATIONS

The cases we are reporting represent a by-product of the clinical appraisal of cutaneous vascular spiders which has been in progress for several years, and comprises observations on almost 350 cases, of which records have been kept on 251.* Many of the early observations, although made independently, merely served to confirm some of those reported by Williams and Snell¹⁷ and Patek, Post, and Victor,¹⁸ and therefore have not been reported heretofore. A few remarks will help in orientation. We have seen vascular "spiders" appear with liver disease of various kinds. In order of frequency, these are Laennec's cirrhosis, catarrhal jaundice, "cardiac" cirrhosis, obstruction of the bile duct by stone, primary hepatoma, rectal carcinoma with hepatic metastasis, hemochromatosis, jaundice caused by arsphenamine and bismuth, fatty liver, unexplained jaundice, and a case of Weil's disease (probable). Although there was, in these cases, a tendency to chronic hepatic disease, vascular "spiders" occasionally appeared after only a few days of illness. On the other hand, we have seen several instances in which spiders were noted years before signs of liver disease appeared. Judging from the nondescript array of hepatic disorders, the type of disease is of no importance; and, from unpublished observations,¹ it can be stated that, although "spiders" tend to appear in persons with *severe or long-standing* liver disease, no known liver function test or clinical feature bears any strict correlation to the development of these vascular lesions. On the average, the worse the liver damage, the greater the likelihood that vascular "spiders" will appear in the skin. Nonetheless, many persons die of liver disease and never have them.

The second group of persons affected with "spiders" consisted of pregnant women. We noted this several years ago, and have observed thirty-seven cases, many of which were seen casually and not followed, since we have not made a routine study of pregnant women. From our records it may be stated that they tend to appear between the second and fifth months of pregnancy, usually increase in size and number until nearly term, and may disappear abruptly within ten days after delivery, although usually the larger ones persist longer and may even become permanent (at least five years). They may reappear or enlarge with subsequent pregnancies. We had supposed that some liver disturbance might explain this phenomenon, but have never found any evidence of past or present hepatic dysfunction that is peculiar to pregnant women who get "spiders," as compared with others who escape these blemishes.

*The early work was done in association with Dr. Donald Forster, and recently with Dr. Morton Hamburger, to whom, along with many house officers and interns, my debt for sundry assistance is very great.

NO.	YEAR	AUTHOR	AGE	SEX	RACE	FAMILY HISTORY	VASC. SPIDERS	LIVER DISEASE	PREG-NANCY
-	1899	Chalmers ⁴	-	M & F	W	-	-	-	-
1	1929	Lane ⁶	51	M	W	+	0	-	-
2	1929	Lane ⁶	69	M	W	+	0	-	-
3	1932	Ambler ⁷	63	M	W	0	0	+	-
4	1933	Mierowsky ⁸	38	M	W	0	0	?+	-
5	1934	Mierzecki ²²	45	M	W	+	0	0	--
6	1935	Gotttron ¹⁰	36	M	W	0	0	?+	-
7	1935	Gotttron ¹⁰	26	M	W	+	0	0	-
8	1936	Kerl ²³	45	M	W	+	0	0	-
9	1938	Bloeman ¹¹	37	M	W	-	0	0	-
10	1939	Schmidt-La Baume ¹²	49	M	W	+	0	?	-
11	1939	Aguilera-Maruri ¹³	54	M	W	0	0	?	-
12	1939	Feldman ¹⁴	32	F	W	0	0	0	+
13	1940	Navarro-Martin ¹⁶	56	M	W	+	0	0	-
14	1941	Walsh and Becker ¹⁵	26	F	W	0	+	0	+
15	1941	Walsh and Becker ¹⁵	23	F	W	0	+	0	+
16	1941	Walsh and Becker ¹⁵	29	F	W	0	+	0	+
17	1941	Walsh and Becker ¹⁵	31	F	W	+	+	0	+
18	1941	Walsh and Becker ¹⁵	37	F	W	+	0	0	In past
19	1941	Walsh and Becker ¹⁵	36	F	W	+	0	0	In past
20	1941	Walsh and Becker ¹⁵	35	F	W	+	0	0	In past
21	1941	Walsh and Becker ¹⁵	59	F	W	0	0	0	0
22	1941	Walsh and Becker ¹⁵	50	F	W	-	0	?	-
23	1942	This series—Case 1	49	F	W	-	+	+	0
24	1942	This series—Case 2	56	F	W	-	0	+	In past
25	1942	This series—Case 3	40	M	W	0	+	+	-
26	1942	This series	60	M	W	0	+	+	-
27	1942	This series—Case 4	45	M	W	0	0	+	-
28	1942	This series	49	M	W	0	+	+	-
29	1942	This series	43	M	W	0	+	+	-
30	1942	This series	49	M	W	0	+	+	-
31	1942	This series	27	M	W	-	0	?	-
32	1942	This series—Case 5	43	M	W	0	+	+	-
33	1942	This series	36	M	W	0	+	+	-
Average			45	Male, 20 Female, 13		40%	36%	50%	81% of females

Since we were altogether ignorant of these eruptive spiders in pregnancy, we searched the standard texts on obstetrics, but found no indication of familiarity with this phenomenon. There are, however, numerous reports in dermatology journals, although apparently no one has succeeded in disseminating this information.

The third group consisted of persons who were known to have, or suspected of having, vitamin deficiency diseases. I have records of 120

I

SYPH- ILIS	SOLES RED- NESS	CLUBBED FINGERS	DURATION	REMARKS
-	-	-	-	In white people in tropics.
-	0	0	Life	-
-	0	0	Life	Thrombophlebitis.
0	0	0	7 years	Began after gall bladder disease.
-	+	0	Months	Developed palmar erythema after a wound of the abdomen.
-	+	0	Life	-
-	0	0	--	Concretio cordis.
-	0	0	Life	-
-	0	0	1 month	Lesions developed while hyperthyroidism was being treated by iodides.
-	0	+	27 yr.	Tuberculous spondylitis.
-	+	0	15 yr.	Dermatographism. Hands had deeper color after ingestion of alcohol.
+	0	0	3 yr.	Tuberculosis and syphilis. The palms gradually cleared after antisyphilitic therapy.
0	0	0	Intermittent	Onset in second and recurrences in 3rd and 4th pregnancy. Fetus had hemorrhages.
?	0	0	Life	Occurred in 3 generations in males only. Onset in 5th month of pregnancy.
0	+	0	Intermittent	Faded after pregnancy, but perceptible 8 months post partum.
0	0	0	Pregnancy	Began in second month of pregnancy and faded by the 9th day post partum.
0	0	0	Pregnancy	Began in the 4th month of pregnancy and was much faded by the 6th week post partum.
-	0	0	Pregnancy	Still present 2 years after pregnancy.
0	0	0	8 yr.	Some pain in hands.
0	0	0	6 yr.	More marked in warm weather.
0	0	0	Life	More marked in warm weather.
0	0	0	6 yr.	Hyperthyroidism.
-	0	0	1 yr.	Hyperthyroidism and diabetes. Palms better after thyroidectomy.
+	-	0	Few wk.	Cirrhosis.
0	-	0	?	Undiagnosed jaundice and hyperthyroidism. ? hepatoma.
0	0	+	Weeks	Cirrhosis.
0	0	0	Weeks	Cirrhosis. Palms faded as jaundice cleared.
0	0	+	2 mo.	Cirrhosis. Mitral stenosis and aortic regurgitation?
0	+	0	Days	Chronic alcohol addiction and lobar pneumonia.
0	+	0	Weeks	Chronic alcohol addiction, lobar pneumonia, and delirium tremens. Palms and spiders faded after pneumonia cleared.
0	0	+	Weeks	Catarrhal jaundice.
0	0	0	Days	Chronic alcohol addiction, jaundice in past. Lobar pneumonia. Color faded after pneumonia was treated.
0	0	+	Unknown	Tuberculous pneumonia, meningitis, epididymitis, and miliary dissemination.
+	0	0	Few mo.	Cirrhosis, proved by autopsy. The palms became red in the last few months of his disease.
14%	20%	15%		

persons with vascular "spiders" who were seen in the Nutrition Clinic in Birmingham, Alabama, during 1940 and 1941. It has not been possible to correlate their occurrence with any known vitamin deficiency syndrome, although, in a few instances, they disappeared after therapy with different vitamin B complex preparations; this may also occur in hepatic cirrhosis.¹ This observation is of questionable significance because the same thing has happened without any therapy or change in

diet, and many "spiders" have persisted in spite of all types of vitamin therapy. They show a notable tendency to occur in children, and there is a strong familial disposition.

Therefore, many or most of those in the third group may rightly belong in the fourth group, which included healthy persons of both sexes and all ages, with no history or suggestion of liver disease, alcohol addiction, pregnancy, or vitamin deficiency. In this normal group it is most difficult to explain the "spiders"; in the other groups there may be a significant common denominator.

From the beginning of this study, very detailed records have been kept on ill persons with "spiders." These include observations on the skin, mucous membranes, and cardiovascular system, and a variety of laboratory studies. Several years ago an example of palmar erythema, associated with vascular spiders and cirrhosis, came under observation and was casually recorded. Not until seeing the second case was our attention sharply focused on the palms. Since then they have not escaped notice, and many patients with other kinds of disease have been inspected for similar changes. In addition to obvious hepatic disease, several instances of palmar erythema have been noted in association with pulmonary disorders, although chiefly among alcohol addicts whose livers were presumably diseased.

The following cases of erythema palmare are presented in detail, so that, if our current interpretations prove erroneous, we shall have clearly defined the background and natural history of the syndrome. It is unfortunate that in the early cases I did not obtain certain details of the history which now seem important. Only after reading the paper of Walsh and Becker¹⁵ was the possible significance of this redness of the hands suspected.

CASE 1 (U-84982).—G. D., a 50-year-old white woman, was admitted to the medical service January 14, 1938, for treatment of pains in the abdomen. She claimed that she had ingested a quart of whiskey daily for twenty years. In recent years she had also taken heroin, and, at the time of entry into the hospital, had been serving a prison term for violation of the Federal Narcotic Law. Her diet should have been adequate, but there were periods when she ate very little. The history was not important in other respects.

Physical examination disclosed a temperature of 98.4° F., a pulse rate of 80, and a respiratory rate of 20 per minute. The blood pressure was 100/65. The enlarged liver presented a smooth, firm border at the level of the umbilicus. It was slightly tender. The spleen was palpable, and its smooth border was a handbreadth below the rib margin. No ascites could be demonstrated. There was no jaundice. The skin of the upper part of the thorax, shoulders, and face was peppered with vascular "spiders;" 43 typical ones were counted. They varied from 5 mm. to 4 cm. in greatest diameter. Dilated vessels were prominent over the nose. The palms showed warm, dusky-red areas, particularly in the hypothenar and thenar regions (Fig. 1). In the red regions the normal pattern of mottling was accentuated, and pale islands stood out against a dark-red, reticulated background.

Chemical studies indicated liver damage. Forty-five per cent of the bromsulphthalein was retained; 3.7 grams of galactose were excreted in testing the

tolerance. The formolgel test was strongly positive. The blood Kalin reaction was strongly positive. The blood cell counts and hemoglobin were normal.

Course.—During her stay in the hospital she became worse, and a new crop of vascular "spiders" appeared. One very characteristic one developed in the site from which another had been removed for histologic study, and several smaller ones appeared, with their centers exactly in the stitch wounds. Later, while she was improving, many of the old and recent "spiders" disappeared and the erythema of the palms faded, but the latter were still more red and warmer than the unaffected adjacent parts. She was discharged after seven weeks; her condition improved considerably during the last month of hospitalization.

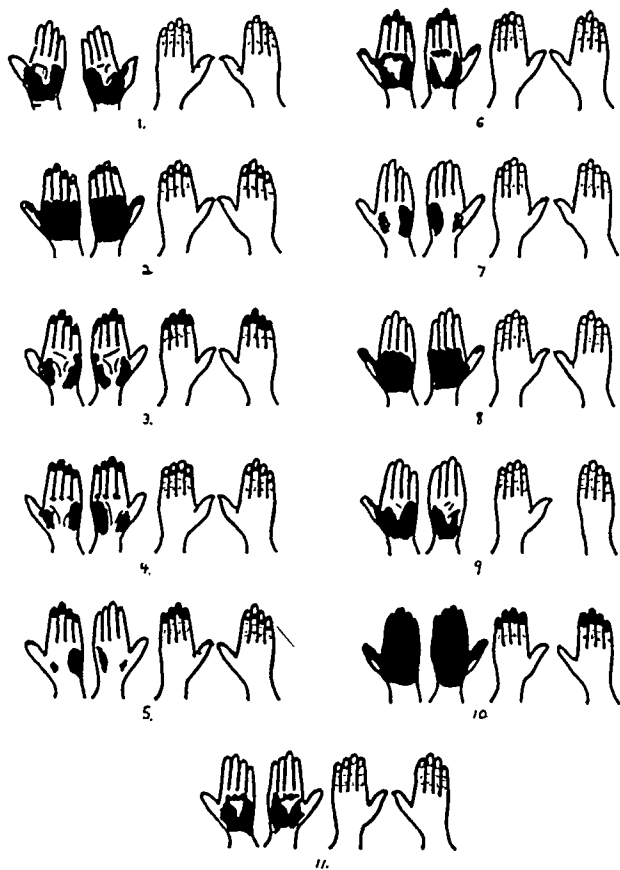


Fig. 1.—Diagrams of the distribution of palmar and digital erythema in the 11 cases. They include Cases 23 through 33 in the table.

CASE 2 (U-157095).—E. E., a 56-year-old white woman, was admitted to the medical service April 4, 1941, complaining of weakness and palpitation which had grown worse slowly for at least two years. There was also a history of exertional dyspnea, dry cough, and yellowness of the eyes of long but unknown duration. Her inadequate diet was further curtailed by anorexia, nausea, and soreness of the mouth. Paresthesias of the hands and feet had also been troublesome.

Examination disclosed an emaciated, icteric, white woman whose thyroid gland was enlarged and contained stony-hard nodules. The tongue and lips were cherry red. There was tachycardia, but no fever. The heart was enlarged to the left, and a harsh systolic murmur was heard at the base. Throbbing of the neck vessels was extreme. The arterial pressure was 150/60, and a capillary pulse was detected. Moist râles were heard at the bases of the lungs posteriorly. Below the right costal

margin the sharp edge of the liver was felt readily, and the spleen came down several centimeters, although the abdomen was not distended. Her palms and finger tips were dusky red and warm to the touch. No vascular "spiders" were seen. Moderate edema of the ankles was present.

The icteric index was 39, the serum albumen, 2.5 per cent, the globulin, 3.2 per cent, and the urea nitrogen, 7 mg. per cent. The erythrocytes numbered 3.9 million, and the leucocytes, 7,000; the hemoglobin was 12.2 grams per 100 c.c. The basal metabolic rate was +55 and +38 on two occasions. More than 30 per cent of the bromsulphthalein was retained at 30 minutes. Free hydrochloric acid was present in the fasting gastric juice.

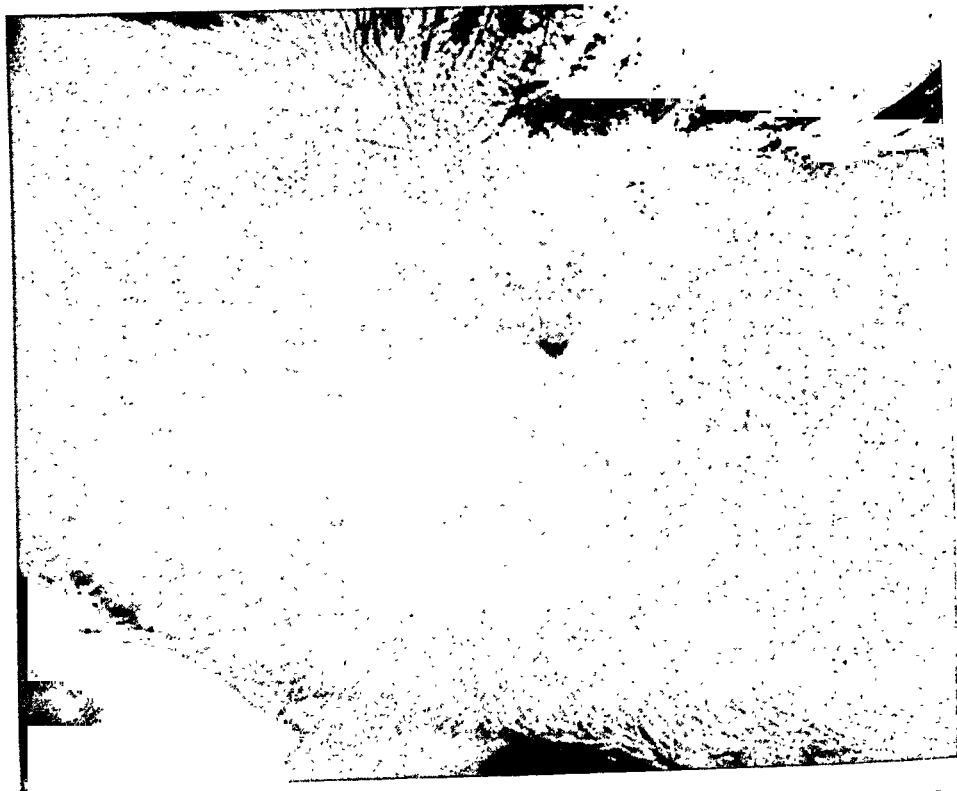


Fig. 2.*—Case 3. This picture shows a large pulsating "spider" which had an elevation of 4 mm. above the surface of the skin of the forehead. In the neighboring regions may be seen the peculiar vascular markings which give the appearance of paper money flecked with silk threads.

Course.—The patient responded to treatment with digitalis, nicotinic acid, thiamin, and riboflavin, although she had auricular fibrillation for several days. The tachycardia persisted, with an average rate of 100 per minute. The administration of Lugol's solution was begun, but, on April 28, she left the hospital because she felt better. Six weeks later she was readmitted in a distressing plight, with edema, dyspnea, and ascites. Her jaundice had increased. On three occasions the serum albumin was 1.5, 1.7, and 0.25 per cent, and the globulin, 6.7, 7.4, and 6 per cent, during the final month. Bone marrow studies suggested a plasma cell myeloma. I did not see her on the second admission, and no note was made about the palms. Her ascites required paracentesis several times. There was gradually increasing liver failure, with deepening jaundice. The prothrombin time was 20 seconds, and the blood urea nitrogen rose to 40 mg. per 100 c.c. She died a month after her second

*The pictures for Figs. 2 and 3 were taken by Mr. J. B. Homan, Associate Professor of Medical Photography, to whom I am greatly indebted for his skill and patience.

admission. The diagnosis was obscure, but the presence of severe liver damage was manifest. No autopsy was done.

CASE 3 (U-165998).—C. B., a 40-year-old white man, a chronic alcohol addict, and a barber by trade, was admitted to the medical service November 2, 1941, complaining of jaundice, edema, swelling of the abdomen, and prostrating weakness which had existed for nearly a month. His diet had been very poor, especially during periodic sprees. He had had a transient spell of painless jaundice at the age of 16. About six months before entry he began to lose energy, and noted edema of the ankles at the end of the day. There was some nausea, particularly in the morning, which he treated by taking a "shot" of whiskey. He had pains and paresthesias in the legs and feet. He stopped work a month before admission, and remained in bed, but the abdominal swelling and jaundice progressed, his urine became dark, and he sought relief in the hospital. The family history was negative; a sister was sure that no one in the family had red hands.

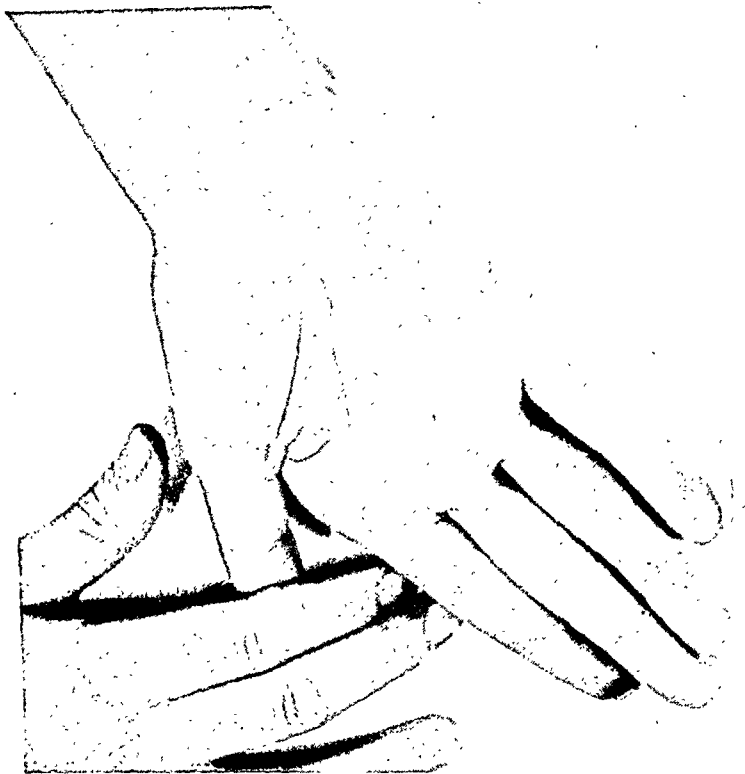


Fig. 3.—Case 3. Palmar erythema is most distinct in the hypothenar area. The sharp but irregular margins are clearly defined. Redness of the terminal phalanges can be made out in the little and index fingers. Mottling of the palm is conspicuous. It will be noted that the erythema is confined strictly to the palmar skin and does not encroach upon that of the wrist.

Physical examination revealed a very ill, deeply jaundiced man; his temperature was 100° F., his pulse rate, 108, his respiratory rate, 22 per minute, and his blood pressure, 140/90. The lips were dusky and the face and chest were warm and moist, and upon the jaundiced skin a dusky red tint was superimposed. There were two, large, pulsating vascular "spiders" (see Fig. 2). Many areas in the skin contained small, dilated arterioles; they were arranged on the chest and abdomen in brushes and chaplets, but had no relationship to the diaphragm or other muscle attachments. In certain regions of the arms there were many similar, short vessels, scattered in disarray which mimicked the apparently aimless pattern of silk threads in American

paper money. The nose also showed tortuous vessels of unusual prominence. There was palmar erythema which was deepest in the hypothenar aspect (see Fig. 3) and dusky red, with irregular, small spots of a paler hue, 2 to 5 mm. in diameter. The red color was present also in the terminal phalanges of all fingers and the thumb, but it cannot be seen clearly in the photograph. There were extreme capillary pulsation in the fingertips, and early clubbing. The chest flared to accommodate the bloated belly, which was well covered with collateral veins. A handsbreadth below the costal margin the firm, nontender edge of the liver was felt. Ascites was present. There was no edema of the legs or ankles, but evidence of peripheral neuritis was found.

The icteric index was 160, and there was a strongly positive direct and indirect Van den Bergh reaction. The prothrombin time was 16 seconds. The blood contained 3.6 units of phosphatase (Bodansky) and 290 mg. of cholesterol per 100 c.c. The erythrocytes numbered 2.6 million, and the leucocytes, 10,000; there were 10.5 gm. of hemoglobin per 100 c.c. Bile was present in the stool and urine.

Course.—The treatment consisted of diuretics, nicotinic acid, thiamin, cod liver oil, and a diet low in fat but high in protein and carbohydrate. It was necessary to resort to abdominal paracentesis Nov. 11 (1900 c.c.), Nov. 16 (3,000 c.c.), and Nov. 20 (1,700 c.c.); there was some seepage from the wound of the second tap. Early vascular changes similar to those in the vascular "spiders" developed about the first paracentesis wound within seven days. The jaundice increased, however, and the patient died on the nineteenth hospital day of hepatic coma. There was no autopsy.

Skin temperature readings were made on the palm at room temperature and at an environmental temperature of 20° C. It was found that the temperature of the areas of erythema ranged from 1.5° to 4.5° higher than the adjacent pale regions of the palm. The temperature of both areas declined and became equal within fifteen minutes after occluding the artery in the upper part of the arm with a pneumatic tourniquet. It was noted that no Bier's spots appeared in the previously red regions, even after forty-five minutes of arterial occlusion. The erythematous skin was more deeply cyanotic than the adjoining skin, and reactive hyperemia was more intense. Temperature measurements over the pulsating vascular "spider" gave readings 2° C. higher than over the neighboring skin; this observation has been made repeatedly on other patients.¹

CASE 4 (U-166406).—L. B., a 45-year-old white man, a chronic alcohol addict, was admitted to the medical service of the General Hospital November 23, 1941, after a convulsion which interrupted a prolonged drinking bout. He had been a heavy drinker since the age of 18, and in recent years had worked in a saloon. He had noticed swelling of his abdomen three weeks before entry, and edema of his ankles developed ten days later. There had been exertional dyspnea. No family history of erythema palmare or telangiectasis could be obtained.

Examination revealed a nervous man who looked older than he admitted being. He was short of breath, and had a warm, moist, cyanotic, yellowish skin. His temperature was 101° F., his pulse rate, 86, his respiratory rate, 28, and his blood pressure, 135/65. The neck veins pulsated. His heart beat was grossly irregular, and the electrocardiogram showed auricular fibrillation. A systolic thrill and the murmurs of aortic stenosis and regurgitation and mitral regurgitation were present, although he did not recall having rheumatic fever. The liver, which was felt with difficulty in his distended abdomen, came down to the umbilicus. Enlargement of the spleen was noted. A few collateral veins stood out on his abdomen. On his chest and shoulders were typical vascular "spiders." His palms and fingertips were involved in the sharply defined, dusky erythema indicated in Fig. 1. There was a mild peripheral neuritis.

The icteric index was 46, the prothrombin time was 21 seconds, and the A/G ratio was inverted (albumin 3.6, globulin 4.0). Examination of the blood showed slight

macrocytosis, but little anemia. Fifteen per cent of the bromsulphthalein was retained after thirty minutes.

Course.—While on the ward his tongue became red, and dermatitis developed on his wrists where shackles had been used. The tongue and skin of the wrists responded to treatment with nicotinic acid, riboflavin, and thiamin, which were used to supplement a diet very high in protein and carbohydrate and low in fat. The jaundice gradually disappeared. The "spiders" on the arms and chest decreased in size, and three disappeared; the erythema of the palms gradually faded until only a faint blush was left in the previously red areas. He was discharged after four weeks.

CASE 5 (U-169539).—J. McG., a 43-year-old white man, was admitted to the medical ward in the last stages of disseminated tuberculosis. There was no story of alcoholism or disease of the liver. He had had the first symptoms of tuberculosis a year previously, and his family physician had found tubercle bacilli in the sputum and cavities in the apices of the lungs. In spite of rest at home, the disease had advanced inexorably. Several months before entry epididymitis set in, and a draining sinus followed. For a few days before admission he was in a deepening stupor.

Examination disclosed signs of widespread pulmonary cavitation, meningitis, and epididymitis. No jaundice was present. The temperature was 102° F., the pulse rate, 150, the respiratory rate, 30, and the blood pressure, 130/104. The fingers were clubbed to an extreme degree, and the erythema of the distal phalanges was extreme. Some osteoarthropathy was present. The palms were universally implicated in the hyperemia. There was one vascular "spider" on the face. Tubercle bacilli in great numbers were found in the sputum.

Course.—After three days in coma he died. The autopsy showed miliary tuberculosis throughout the body, although the liver was not without large areas of normal looking tissue. Much of the lungs had been destroyed.

DISCUSSION

These patients with palmar erythema had diagnostic or presumptive evidence of liver disease. No history of a family tendency to palmar erythema could be obtained, but, since some patients were evasive about the past and vague about the present, this observation is unreliable. The presence of vascular "spiders" in eight cases is of great interest, especially because they tended to wax or wane in phase with the variations in the hyperemia of the hands. There was a definite correlation between the fluctuation in severity of the liver disease, as judged clinically, and the advance or regression of the "spiders" and the palmar erythema. This suggests that whatever evokes or suppresses the one behaves in like fashion towards the other. Together with many other facts, it also points to the probability that a humoral mechanism underlies these two vascular phenomena. In the surveyed cases (excluding those associated with pregnancy), liver disease or a familial tendency to redness of the palms existed; sometimes they occurred together. In some subjects this sign had existed for years, and was unaccompanied by symptoms. In others it appeared after the onset of some illness, perhaps to fade away when health returned.

The nature of this alteration in blood flow in the skin of the hand is obscure. Since it is not necessarily permanent, it undoubtedly consists of a reversible change in local palmar circulatory adjustments. It re-

mains to consider the reasons for the curious localization and the possible cause of the erythema.

Information on the comparative histology of the skin, nerves, and blood vessels of various parts of the palm and sole is scant. It is well known that these regions are more vascular than the neighboring portions of the skin on the arms and legs, but the vascular architecture of different areas of the palm and sole has not been mapped. The presence in the palms and soles of large numbers of direct arteriovenous shunts is significant. Since the increased redness is associated with an increase in surface temperature, the blood flow must be increased. Capillary pulsation, which is so prominent in the finger tips and manifest in the palms, also attests to an open state of the vascular bed in the erythematous region. We have found no increase in the systemic circulation time (decholin) and, with rare exceptions, none in the arterial blood pressure, which indicates that the enhanced blood flow is a local phenomenon and is probably restricted to the skin. A variation in the depth of color from time to time, and the occurrence of a dusky cyanosis on occasions, emphasize the lability of the basic physiologic alteration. According to Walsh and Becker,¹⁵ the overlying skin is not thinner than normal. There is, however, definite dilatation of the palmar capillaries, and many more than the normal number can be seen under the capillary microscope.

The pattern of redness, although the intensity of color fluctuated, was permanent in outline in each of our cases. Among the patients there was much variation in the extent and distribution of the erythema (see Fig. 1). As Chalmers⁴ pointed out, no cutaneous nerve supplies the exact area involved. Similarly, the large anastomosing arterial arcades are not limited to the strict confines of the red regions. One must conclude that other local anatomic factors are concerned. Innervation by the sympathetic nerves might possibly explain it, or some structural constant, such as arteriovenous anastomoses, but this cannot be settled on the basis of available data.

The strong thread of familial predisposition stands out. This could mean an inherited structural fault, actual or potential, which allowed the vascular changes to occur under the proper stimulus. Or it might signify unusual susceptibility to the exciting mechanism, a susceptibility perhaps not present in normal persons. The hereditary and familial factors need much more careful study before conclusions may be reached. They were not found in our cases, but the history was not often conclusive. The possible relation to the familial tendency to vascular "spiders" in apparently normal persons¹ should be investigated.

Even if we assume that an anatomic disposition to erythema palmare exists, the exciting cause demands careful scrutiny. Because it and its congener, the cutaneous vascular "spider," vary under the same

clinical influences, we have searched for some physiologic disorder common to both. Study of the vagaries of the vascular "spider," especially the evanescent type which occurs with liver disease and pregnancy, aroused the suspicion that the exciting cause of these eruptive vascular phenomena might be a protracted increase in circulating estrogens or the related 17-ketosteroids. An excess of estrogens is a well-known phenomenon of pregnancy, and it occurs at about the time the "spiders" make their appearance.¹ Not so well known, but nonetheless certainly established, is the fact that the liver normally destroys, changes, or inactivates estrogens.¹⁹ It has been shown that, at least in some cases of cirrhosis, large quantities are excreted in the urine, sometimes in unusual form.²⁰ Thus the common denominator of acquired vascular "spiders" may reside in prolonged alteration of the circulating 17-ketosteroids; the relationship is certainly quantitative, and perhaps also qualitative, whether in pregnancy or hepatic disease. If this speculation be correct, it is reasonable to assume that the same thing brings out the acquired erythema of the palms in subjects who are predisposed. Lending some weight to this assumption is the observation of Edwards, Hamilton, Duntley, and Hubert,²¹ who used the Hardy recording spectrophotometer to study the changes in the concentration of hemoglobin and oxyhemoglobin in the skin of castrate and eunuchoid men before, during, and after treatment with a 17-ketosteroid, testosterone propionate. They obtained objective and quantitative data which verified their clinical impressions concerning the changes in the skin. Of especial interest in connection with our observations on acquired erythema of the hands (and sometimes feet) was their finding that the normally very pale skin of castrates developed a ruddy hue after ketosteroid therapy. The change was particularly marked in the *palms*, *soles*, and other regions of the skin which are well supplied with arteries. They demonstrated the arterial nature of the blood, with its high content of oxyhemoglobin, and gave reasons for believing that the local blood flow was increased in volume and rate. We have produced evidence that such a state obtains in the red areas of the palms.

The associated clubbing of the fingers in four of our eleven cases deserves comment. In some instances the degree of clubbing varied with the intensity of hyperemia in the finger tips, although the nails changed more gradually than did the digital erythema. The idea that clubbing depends on an increase in blood flow, or a change in the pressure gradient in the arteries, has been suggested in the past. The occurrence of clubbing of the fingers in association with liver and thoracic disease may depend upon the same alterations in circulation which give rise to the palmar and digital hyperemia.

CONCLUSIONS

Study of the acquired vascular "spider" and acquired palmar hyperemia suggests that these vascular alterations are caused by an increase

of the circulating 17-ketosteroids. We assume that the small arteries of susceptible regions of the skin in predisposed persons become widely patent, allowing an influx of arterial blood. In the case of the cutaneous vascular "spider," this may take the form of a small arterial aneurysm. In the palm, general arterial dilatation develops, perhaps with opening of many arteriovenous shunts. We have had no opportunity to study the metabolism of estrogens and related compounds under the circumstances in which these vascular changes occur, but there is ample evidence of an increase in the amount of estrogenic 17-ketosteroids in the blood and urine in liver disease and pregnancy. Because of the elaborate and treacherous technique required, it seemed unwise to undertake assays. We have, however, administered estrogens to some of our subjects whose palms or "spiders" had faded. In two instances the "spiders" reappeared, and in one case the palms became red for the first time.²⁴ In the absence of any quantitative studies on estrogens, and because the suggestions put forward are supported only by clinical analogy, we hesitate to solidify these ideas into any rigid hypothesis. The pituitary gland has been omitted from consideration altogether, rather from ignorance than belief that it is unimportant. Further implications of this thesis are apparent, and have important bearing upon such phenomena as the association of Hippocratic fingers and digital erythema, the infrequent clinical association of cirrhosis and arteriosclerosis, and other obscure relationships.

SUMMARY

1. The literature on erythema palmare has been reviewed.
2. Eleven new cases are reported in patients with hepatic or pulmonary disease, or both. Contrary to the experience of others, no familial tendency was discovered in these cases.
3. Cutaneous vascular "spiders" occurred in eight of the eleven cases. These lesions waxed and waned concomitantly with the degree of redness of the palms.
4. It is postulated that both of these localized vascular disturbances result from an abnormality in circulating estrogenic substances and other 17-ketosteroids.
5. Experiments to test this hypothesis suggest that it may be valid, although not enough data are available for final conclusions.

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ADDENDUM

In a discussion of my paper on Vascular Spiders and Palmar Erythema at a meeting of the Central Society for Clinical Research, Chicago, Ill., Nov. 6, 1942, Lt. Col. P. S. Hench called attention to his work on the ameliorating effect of jaundice and pregnancy upon certain forms of arthritis, and suggested that a similar mechanism might underlie this phenomenon and the emergence of "spiders."

PATHOGENESIS OF SUBACUTE BACTERIAL ENDOCARDITIS

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SUBACUTE bacterial endocarditis was first described in this country as a clinical entity by Libman¹ at about the same time that Schottmüller² recognized it abroad. As early as 1909-10, Libman and his associates, notably Celler³ and Baehr,⁴ made thorough pathologic, bacteriologic, and clinical studies which elucidated the salient features of the malady and permitted its early clinical recognition.

Because the disease is insidious, Schottmüller named it *endocarditis lenta*, and stated that the *Streptococcus viridans mitis* is the sole cause of the infection. It is agreed that in the majority of cases the *Streptococcus viridans* is the direct etiologic factor. However, as was first pointed out by Libman and his co-workers, and later universally confirmed by Herrick,⁵ Hamman and Rich,⁶ Thayer,⁷ and Horder,⁸ it is now known that other microorganisms can be responsible for this form of endocarditis. Not only can any microorganism produce the disease, but not infrequently two or three different bacteria may be recovered from blood cultures and from the diseased valve. Orgain and Poston⁹ described five cases of mixed infection in bacterial endocarditis. The individual cases recently described (De La Chapelle and Graef,¹⁰ Spink and Nelson,¹¹ Wechsler and Gustafson¹²), in which the endocarditis was caused by the *Brucella* organism, indicate that the rarest types of microorganisms may also cause subacute bacterial endocarditis. It is therefore appropriate to adhere to the name proposed by Libman, i.e., *subacute bacterial endocarditis*.

The most thorough investigation of the pathogenesis of the disease has failed to yield the answers to many fundamental questions. Why does subacute bacterial endocarditis affect only a diseased valve? Why does the damaged valve often enjoy immunity from the disease for many years, and then suddenly become vulnerable? Why does the disease last so long, and why does it almost always end fatally?

It has been assumed by the older classical theorists that the illness is protracted because the *Streptococcus viridans* is less virulent than most other pathogens. A priori, this does not appear reasonable, for other microorganisms, as stated above, which are otherwise very virulent, such as the *Streptococcus hemolyticus*, the gonococcus, the pneumococcus, the meningococcus, and Friedländer's bacillus, can cause the same pathologic changes in the valves and the same drawn-out clinical course. On the other hand, the *Streptococcus viridans* may cause acute fulminating endocarditis, with death in two to seven weeks, as in the case of four

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patients at the Beth Israel Hospital¹³ who were weakened by serious previous illnesses. The virulence of the organism appears, therefore, to be a much less important factor than the natural resistance of the host.

Another view of the pathogenesis of this disease was expressed by Clawson and Bell,¹⁴ who are of the opinion that rheumatic endocarditis and subacute bacterial endocarditis are merely mild and severe forms, respectively, of the same infection. Von Glahn and Pappenheimer¹⁵ added support to this view by their contention that subacute bacterial endocarditis is usually implanted on recently active rheumatic lesions, and not on old or healed rheumatic valvular defects. To refute this concept of the pathogenesis of subacute bacterial endocarditis, we need only consider that the influenza bacillus, the pneumococcus, the gonococcus, and numerous other organisms can cause the disease, and surely these organisms have no relationship to rheumatic fever. Furthermore, in the majority of cases there is no pathologic evidence in the myocardium, such as the presence of Aschoff bodies, or in the pericardium, of recent rheumatic infection. Of course there is no doubt that rheumatic valvular disease is a vital predisposing factor, but its immediate relation to subacute bacterial endocarditis is undoubtedly the exception rather than the rule. It is also well known that, occasionally, syphilitic aortic valvular disease may be the forerunner of subacute bacterial endocarditis, and congenitally deformed valves likewise predispose to this fatal infection. As far as is known, congenital valvular defects are certainly not the result of rheumatic infection.

Grant, et al.,^{16, 17} and Keefer¹⁸ have advanced the theory that platelet thrombi on the previously damaged heart valve serve as a nidus on which the bacteria deposit themselves, thrive, and initiate subacute bacterial endocarditis; they assume that, in order that bacteria may lodge on the previously diseased, deformed valve, a thrombotic valvular lesion must pre-exist. Despite the plausibility of such a concept, we are confronted with the following questions: (1) What is the original cause of such blood platelet thrombi, and (2) why do they occur in some cases of damaged valve and not in others? Furthermore, what is the origin of such blood platelet thrombi in a congenital heart lesion or on a congenitally bicuspid aortic valve? We know that, at autopsy, in the majority of cases of congenital heart disease and recurrent endocarditis and heart failure, no thrombotic lesions are seen, and terminal thrombotic endocarditis is quite common in wasting diseases and other agonal states, but subacute bacterial endocarditis does not occur in these cases. Furthermore, subacute bacterial endocarditis does not superimpose itself on the thrombotic endocarditis described by Friedberg, et al.¹⁹ Therefore, why should we assume that a thrombotic lesion

*Recent studies in the laboratory of Dr. Paul Klemperer, Mt. Sinai Hospital, N. Y., by Dr. Arthur C. Allen, show definitely that what is called thrombotic endocarditis is pathologically not thrombotic because blood platelets and fibrin are conspicuously absent. The lesion, as shown by Allen, is a degenerative endocardial change; similar areas are found also in the myocardium in chronic wasting diseases and terminal infections.

exists on some rheumatic valves and not on others? It is more reasonable to assume that, in subacute bacterial endocarditis, if section shows some thrombosis along the edge of the valve, this is only part of the active pathologic process, and not the pre-existing cause.

It seems to us that the peculiar pathologic changes and clinical course of this disease can be attributed to local tissue reactivity caused by hyperimmunity. The local and systemic tissue resistance and the immunity of the reticuloendothelial system in general, and of the endothelium of the valves and heart in particular, are responsible for the protracted course. Death occurs only when there is exhaustion of the endothelial system, unless some complication, such as embolism, or rupture of a mycotic aneurysm in the brain or in the subarachnoid space, terminates the disease earlier. The endothelial nature of the disease thus asserts itself. So prominent is the invasion of the endothelial system in this disease that one may even speak of it as infectious endotheliosis, in analogy to what E. Frank terms, among the diseases which manifest a hemorrhagic diathesis, "hemorrhagic endotheliosis."

That the reticuloendothelial system plays an immense role in the production of immunity was well established by the studies of Metchnikoff, Aschoff, Goldmann, Ehrlich, and others. Recently, Sabin,²⁰ in a brilliant piece of work, demonstrated microscopically the formation of antibody globulin in the cells of the reticuloendothelial system, which emphasizes the prime importance of the endothelial cell in resisting infection. The body reaction to infection is thus determined largely by the state of the reticuloendothelial system, and can be conveniently classified, as Siegmund²¹ and Dietrich²² suggested, into three general types: the a-reactive, the normally reactive, and the hyperreactive. In the a-reactive type, which occurs with fulminating infections, there is complete loss of reactivity, so that any microorganism in an insignificant focus may so overpower the body as to cause death without localization of the infection at the focus, and before any appreciable pathologic change can occur ("cryptogenetic sepsis"). In contrast to this, in the normally reactive type of infection, the immunity of the body permits localization of the infection. In the hyperreactive, the tissues have become highly immunized against a microorganism, and there is a marked local reaction at the site of invasion, with the advantage in the struggle largely on the host's side. We believe that this last type of reaction, i.e., that of tissues highly immunized by previous infection, explains the lesions and clinical course of subacute bacterial endocarditis. If the lesions were not located in the heart, whence broken-off vegetations are carried to distant parts of the body, either with or without bacteria, the outcome would not necessarily be fatal. When considered as a hyperimmune reaction to infection, the pathologic changes responsible for the symptoms in this disease can be easily understood. We shall attempt to review them in this light, one by one.

The disease begins during the transient bacteremia that accompanies most infections (pyelitis, tonsillectomy, extraction of an infected tooth, etc.), affecting first the capillaries of the valve. Because of the hyperimmunity and increased local resistance in chronically diseased valves, the usual response to infection, such as exudation of leucocytes, ulceration, and connective tissue formation, does not occur, but, instead, there is a deposit of fibrin and blood platelets similar to that which follows a clean skin incision. This fibrin, blood platelet thrombus constitutes the soil on which the circulating bacteria implant themselves. Polypous vegetations form and tend to remain localized or spread by contiguity to different parts of the heart—in mitral stenosis, to the auricle, and, in aortic disease, to the ventricle, or even to another valve.

In contradistinction to the theories of the above mentioned authors, and particularly that of Keefer, who considers the thrombotic lesion to be the primary factor, it is our concept that the thrombus is caused by the action of the bacteria on the capillaries of the diseased valve, and that it is from these capillaries that the blood platelets and fibrin escape. On this thrombus more bacteria deposit themselves, forming additional vegetations. Thus a septic focus develops on the heart valve, which, as a rule, gives rise to secondary foci in other parts of the body. Following this viewpoint, we may say that *subacute* bacterial endocarditis constitutes an "endocardial sepsis," whereas *acute* ulcerative endocarditis can be termed "septic endocarditis." In the latter, pathologic changes in the endocardium are a part of those in the rest of the body; whereas, in the former, all the changes that take place in the rest of the body are caused by the original focus in the endocardium. The changes in the capillaries and arterioles, as well as those which occur occasionally in the larger blood vessels, are caused either by direct embolism from the endocardial vegetations, with or without bacteria, or by toxins. In either event, aneurysmal dilatation and rupture of small capillaries or arterioles may result. In other instances, vascular obstruction may occur, e.g., in the larger vessels of the lower extremities, leading to gangrene, or sudden obstruction, by bacterial emboli, of the coronary or mesenteric vessels. Aneurysmal dilatation in the brain may lead to cerebral or subarachnoid hemorrhage.

Since the embolus usually comes from the left side of the heart, pulmonary infarction does not often occur, but renal and splenic infarction is common. The truly bacterial emboli have a tendency to involve the larger blood vessels (arterioles), whereas the toxins tend to affect the capillaries. In most instances the petechiae are caused by the impairment in the permeability of the capillaries which results from the toxic effect of the bacteria.

The manifestations of embolism depend largely on the size of the vessel. If it is in small capillaries (as the conjunctivae), it causes the characteristic white-centered petechiae, whereas in larger vessels it forms little nodes (Osler nodes) which have a great tendency to be

absorbed. When it attacks the endothelial layer of the glomerulus, it causes the characteristic Lohlein-Baehr glomerulonephritis. This is a progressive kidney lesion which shows, as is the case in all other organs, no tendency to connective tissue formation. Since neither the afferent or efferent vessels of the kidney suffer, there is no increase in blood pressure. The pin-point hemorrhages in the glomeruli give rise to the typical "flea-bitten" kidney. Christian²³ reported studies on the kidneys of sixty-one patients who died from subacute *Streptococcus viridans* endocarditis. He found areas of infarction in 91.8 per cent, proliferative, cellular, glomerular lesions which were analogous to the lesion in acute intracapillary proliferative glomerulonephritis in 80.32 per cent, and diffusely distributed, hyaline thickening of the walls of the glomerular capillaries in 16.39 per cent. He encountered five types of glomerular lesions: (1) proliferation of the capsular epithelium, (2) focal fibrous lesions, (3) complete disorganization of glomeruli, (4) hyalin fibrinoid thrombi in glomerular vessels, and (5) masses of bacteria in glomerular capillaries.

In short, this is a disease which, either by bacterial vegetations or toxins, affects first the endothelium of the endocardium and valves, and then the endothelial structures of capillaries and arterioles of different parts of the body. The outcome of the disease can be explained by the degree of that invasion.

In the majority of cases there is mild sepsis. The patient is not "heart-conscious." Only because of the protracted fever, the presence of valvular disease, and the moderate anemia does the physician suspect the possibility of this disease. In the majority of cases our attention is called to involvement of the capillaries by the petechiae in the conjunctivae, mouth, or elsewhere. In the finger tips there may be the painful Osler nodes (known also as Libman nodes). In most cases the endothelial system of the spleen responds actively, so that there are enlargement and induration of this organ. In acute infections, on the other hand, the spleen is soft and tender.

Another early and frequent manifestation is hematuria. Although this accompanies gradually increasing involvement of the glomerular capillaries, it is usually associated with very little albuminuria, only occasional casts, and no change in the specific gravity; usually, there is no increase in the blood pressure.

In many cases, clubbing of the fingers develops quite rapidly as a result of capillary changes in the nail bed. When the disease is protracted, the endothelium of the hemopoietic system (bone marrow, etc.) is involved. As in subleucemic leucemia, there may be leucopenia, with immature leucocytes (myelocytes and myeloblasts) in the blood.

There is every reason to believe that, in some cases, healing and recovery occur, as Libman has reported. When blood cultures are taken often enough in the acute phase of the disease, the organism will be found in more than 90 per cent of the cases (Libman and

Friedberg²⁴). The degree of bacteremia, that is, the number of colonies found on culture, does not indicate how soon the disease will end fatally, although in the terminal stage the number of colonies increases rapidly. There are on record a number of cases of two or three years' duration in which there were numerous colonies in the blood culture. On the contrary, in the healed stage (Libman), when the blood cultures are persistently negative and even when no bacteria are found in the diseased valve post mortem, there may be marked anemia and uremic manifestations caused by diffuse glomerular disease, but no increase in blood pressure.

The disease occurs typically in patients with rheumatic heart disease who, after the original infection, apparently acquired enough immunity to insure against reinfection. In contrast to other cases of rheumatic fever, in most of the cases of subacute bacterial endocarditis recurrent rheumatic endocarditis is the exception. It is also important that, even during the first acute attack of rheumatic fever, such patients have very few cardiac manifestations, so that sometimes the patient cannot recall having been afflicted with valvular disease, unless his attention had been called to the existence of a murmur. Neither the myocardium nor pericardium was involved, and therefore there were no cardiac symptoms. This is also the reason why, in these cases, a history of congestive heart failure is rare, nor does it occur in patients with auricular fibrillation. One encounters cases in which there is no history of rheumatic fever, although, in his youth, the patient may have had mild growing pains in the muscles or extremities, or, after a mild attack of scarlet fever or pneumonia, may have been left with a valvular lesion which produced no important symptoms. There are exceptional cases, as, for instance, those reported by Grossman and Lieberman²⁵ and Segal,²⁶ in which auricular fibrillation and subacute bacterial endocarditis coexisted. We believe that, in these cases, as a rule, congestive heart failure does not account for the fibrillation, but that the vegetation invades the mural endocardium of the auricle, causing fibrillation without signs of congestive heart failure.

If there is increased resistance and hyperimmunity in these cases, what permits the subacute bacterial infection to start on the diseased valve? We feel that the insidiousness of the disease indicates that some other infection acts as a forerunner for subacute bacterial endocarditis. There is often an upper respiratory infection caused by the influenza bacillus or pneumococcus, during the course of which the *Streptococcus viridans*, which is found so widely distributed in the body, enters the blood stream, lodges on the diseased valve, and forms the nidus of the subacute infection. It is known, further, that, after tonsillectomy, cystoscopy, or extraction of an infected tooth, there is often a transient bacteremia which may do no harm to the normal person, but, when a valvular lesion is present, the circulating bacteria may lodge on the valve and start the infection. Such a concept suggests that, if we attack

the disease in its very early stage with chemotherapeutic measures, as recently suggested by Christian, we may be able to abort it. Ordinarily, one sees the patient late in the course of the disease, when the endothelial system and other organs are so affected that the chemotherapeutic agent cannot reach all the bacteria and may do more harm than good. Our hope lies in discovering the disease early, before the endothelial system has become irreversibly exhausted, and before complications have set in.

SUMMARY

Subacute bacterial endocarditis is a distinct pathologic and clinical entity. The vegetative endocarditis that characterizes this disease, with its exudation of fibrin, blood platelets, and enmeshed bacteria, represents a state of high local and general tissue immunity to bacterial invasion, rather than lowered resistance; the immunity resides in the local endothelial structures, as well as in the general reticuloendothelial system. Since the reaction to this bacterial invasion is largely endothelial, the disease can rightfully be termed *infectious endotheliosis*.

Subacute bacterial endocarditis occurs typically in patients who have valvular disease, usually rheumatic, but who have acquired a high degree of immunity, so that reinfection, recurrent endocarditis or pancarditis, and congestive heart failure do not occur. This increased immunity is responsible for the fact that the patient is not heart-conscious even during the attack of acute valvular infection. Then a transient bacteremia, caused by an upper respiratory infection, tonsillectomy, the extraction of an infected tooth, or pyelitis, permits secondary invasion and implantation of bacteria (usually the ubiquitous *Streptococcus viridans*) on the damaged valve. A careful history will reveal that some infection which lowered the general body resistance is usually the beginning of an illness that later develops into subacute bacterial endocarditis. Although the bacteria are able to implant themselves on the damaged valves, they find in the valve an altered tissue reactivity which does not permit much local damage, such as ulceration or extension into the myocardium or pericardium. A more favorable outcome would be likely if the bacteria were not localized in a focus that communicates directly with the blood stream. If embolism does not cut the disease short, death occurs when the local and systemic endothelial systems become exhausted.

Subacute bacterial endocarditis is a true endocardial sepsis, for the valve acts as the primary distributing focus of the infection. As such, if the focus can be removed surgically (as in some cases of patency of the ductus arteriosus) or chemotherapeutically before complications set in, there is some hope for a cure of this dreaded disease.

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THE ROLE OF INSULIN-FREE, HISTAMINE-FREE PANCREATIC TISSUE EXTRACT IN THE TREATMENT OF PERIPHERAL ARTERIAL DISEASE*

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IN 1928, Frey and Kraut¹ described a physiologically active substance which is excreted in the urine and is normally present in large quantities in the pancreas. The intravenous administration of this material to animals produced a transitory fall in blood pressure, an increase in the cardiac rate, and an increase in the stroke volume. Gley and Kisthinos,² working independently, isolated an insulin-free material from the pancreas which had the property of producing a transitory fall in blood pressure after intravenous administration, and also antagonized the pressor effects of epinephrine. In neither case could the physiologic effect be attributed to histamine, choline, or peptone. This question has been raised by Villaret, Justin-Besançon, and Cachera,³ who felt that the crude preparations with which they were working contained a sufficient quantity of choline and histamine to account for the cardiovascular action. More recently, Elliot and Nuzum,⁴ using a more highly purified preparation, were able to demonstrate that the physiologic activity of their material was not due to the presence of histamine, choline, or peptone.

Wolffe and his co-workers,⁵ because of certain superficial similarities between the action of this type of pancreatic tissue extract and the so-called heart muscle extract, suggested that the activity of the former might be attributed to the presence of adenosine, adenylic acid, or some allied substance. Both adenylic acid and adenosine, in addition to a transitory fall in blood pressure and an increase in coronary flow, cause transitory heart block when administered intravenously. This last action is so uniform that Drury and Szent-Györgyi⁶ suggested that it be used as a biologic method of identification of these substances. We have administered the pancreatic extract to be described, in doses as high as 100 units, intravenously to dogs, without producing heart block. Similar negative observations were made on anesthetized guinea pigs. This is in accord with the observations of Elliot and Nuzum⁴ on rabbits and guinea pigs.

Clinically, the material has been used widely. Vaquez, Giroux, and Kisthinos⁷ and Wolffe⁸ have reported favorable results in the treat-

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ment of angina pectoris. The European literature contains a considerable volume of confirmatory clinical observations, but much of this is based on symptomatic relief of ill-defined clinical entities.

Wolffe and Digilio⁹ analyzed a series of 108 patients with hypertension who were treated with a similar pancreatic tissue extract. Less than 8 per cent of the group showed any significant lowering of the systolic and diastolic blood pressure after medication; more than 60 per cent, however, showed symptomatic relief which persisted for more than a year. Fisher, Duryee, and Wright,¹⁰ working with a carefully studied series of cases of clearly defined vascular disease, under controlled experimental conditions, were able to show that such tissue extracts materially prolonged the time required for the onset of claudication when the patients were subjected to standardized physical exertion.

During the course of the last few years the original methods for the extraction and isolation of the active principle have been so improved that a highly potent, stable preparation has been made available.⁶ This material, which will be described in detail elsewhere,¹¹ was prepared by a modification of the process used by Werle and Urhahn,¹² and contains approximately 15,000 units per gram. Lyophilized preparations lost no activity after being kept at 37° C. for a period of two hundred seventy days.

Finely-ground, fresh or frozen hog pancreas is suspended in water, the pH of the mixture is adjusted to 8.0, and the mixture is digested with trypsin at 37° C. Toluene is used as a preservative. The trypsin destroys all the insulin in the suspension. The mixture is then acidified with trichloroacetic acid, and ammonium sulfate is added to one-third of saturation. The insoluble matter, which consists of fibrous tissue, fat, undigested proteins, (primary) proteoses, and trypsin, is centrifuged off and discarded. The clear, supernatant solution is then brought to saturation with ammonium sulfate, and the crude precipitate formed thereby is centrifuged off. (The saturated ammonium sulfate mother liquor retains peptones, amino acids, and any histamine or choline which may be present.) The crude precipitate is then dialyzed under toluene in cellophane tubes against distilled water until it is free of sulfate (dialysis effects the removal of ammonium sulfate and of any histamine or choline which may have been adsorbed on, or included with, the crude precipitate). The water is finally removed by the Niphanoid process (dehydration of frozen extract under high vacuum).

Standardization.—In our experience, neither the procedure of Gley and Kisthinos² nor that of Frey and Kraut¹ is dependable for the assay of the active principle. In the first instance, the unit was considered that quantity which, when injected intravenously into a 2.0 kg. rabbit, caused a barely perceptible fall in the blood pressure; in the second instance, it was defined as that amount which caused an increase in the amplitude of cardiac contraction of one minute's duration. We encountered such wide variations in potency with both of these methods of biologic assay that we felt the need of devising one which would be more reliable. In our experience, the most dependable animal for this procedure is the dog. The unit, as we define it, is that quantity of the active principle which, when injected intravenously into an atropinized dog under sodium barbital anesthesia, will exactly counteract the pressor effect of a minimal hypertensive dose of epinephrine. Since

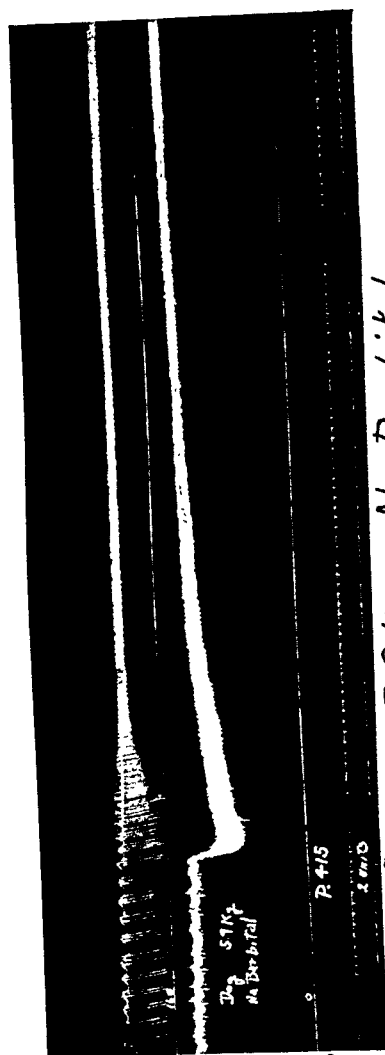
*Tissue extract—P-415—obtained from the Research Laboratories, Winthrop Chemical Company, Inc., Rensselaer, N. Y.

dogs under comparable conditions vary widely in their vasomotor response to epinephrine, this minimal hypertensive dose must be established for each animal. We have found that the required amount varies between 15 and 50 micrograms for dogs of 10 to 15 kg., although the dose is not proportional to the weight. It should also be pointed out that this minimal hypertensive dose varies with the tone of the vasomotor system. Large or repeated doses of the tissue extract depress the tone of the peripheral vasomotor system, as indicated by alteration of the threshold dosage of epinephrine. Successive doses of one or more units of this extract should therefore be spaced at intervals of at least fifteen minutes in order to allow for recovery. In practice, this factor is largely corrected by allowing a sufficient period to elapse so that the threshold for normal epinephrine responses (indicative of a normal autonomic equilibrium) is re-established. Three animals are used for each assay. The standard unit may be defined as that quantity of the extract which will neutralize the pressor effects of 30 micrograms of epinephrine.

EXPERIMENTAL OBSERVATIONS

1. Dogs. All observations were made on atropinized dogs under sodium barbital anesthesia. The intravenous administration of the active principle in small doses (1 to 2 units) produces a transient fall in the blood pressure, of the order of 30 to 45 mm. Hg, which persists for about ten minutes. This fall in blood pressure is accompanied by a marked increase in pulse pressure, and, as indicated by Greene,¹³ this effect is associated with marked coronary dilation. Using a constant temperature plethysmograph and a photoelectric recording system, which are described in detail below, we have been able to demonstrate that the initial fall in blood pressure is accompanied by a marked increase in limb volume, and that this increased volume is still evident long after the initial blood pressure level is re-established. A sharp fall in blood pressure follows the intravenous administration of 2 units of the active principle, and with this there is an increase in pulse pressure (Fig. 1). This occurs immediately after administration; the normal level is re-established within nine minutes. Below this there is a simultaneous record of the changes in limb volume. The first part of this record shows the normal volume; the second portion of the record starts at the time of injection, and shows the increased volume associated with the fall in blood pressure. This increased volume persists long after the blood pressure has returned to its normal level; the third portion of the record, which was made fifty minutes after the injection, shows that the peripheral dilatation is still present.

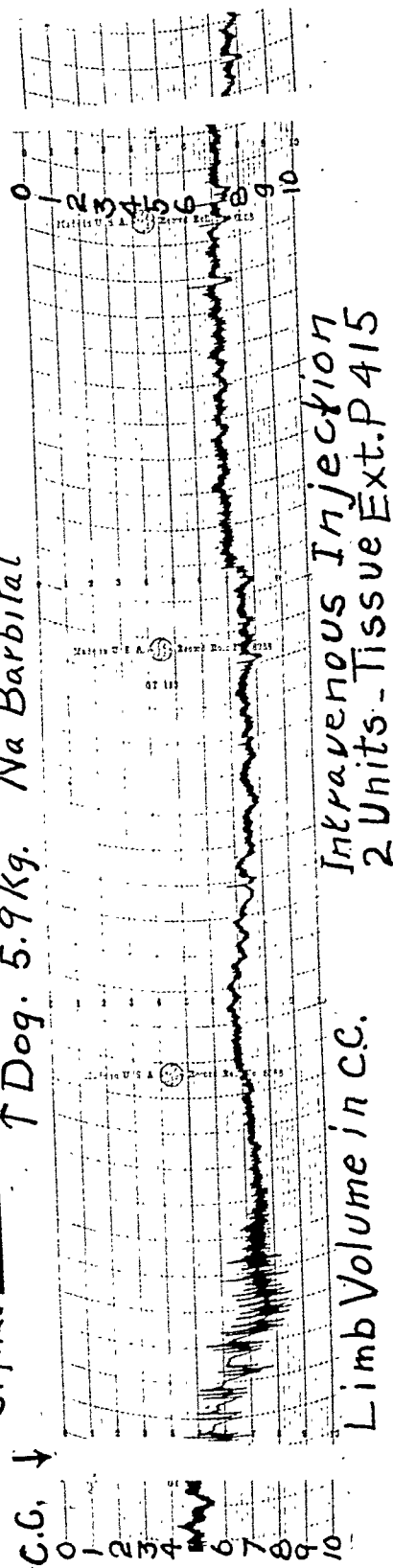
When the active principle is administered intramuscularly, there is no appreciable effect on the blood pressure. Giving doses as large as 80 units to a 15 kg. dog produced no fall in blood pressure over a period of seventy-five minutes. However, such doses produced a persistent increase in limb volume. Fig. 2 shows this clearly. The intramuscular administration of 20 units of the active principle failed to produce any demonstrable change in the blood pressure of a lightly anesthetized dog. The injection, however, was associated with a prompt increase in limb volume which persisted for a period well in excess of thirty minutes.



Resp.
B.P.

Time-10"
Signal

↑ Dog. 5.9 Kg. Na Barbitol



Limb Volume in C.C.

Fig. 1.

Resp.

B.P.

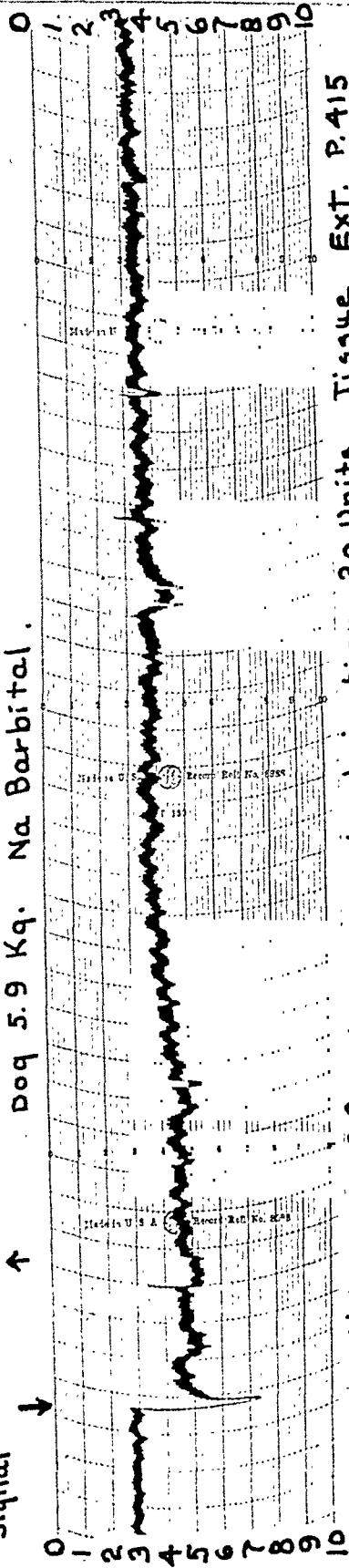
Dog 5.9 Kg
Na BARBITAL

P.415

Time - 10"

Signal

↑ Dog 5.9 Kg. Na Barbitol.



Limb Volume in C.C. Intramuscular Injection 20 Units. Tissue Ext. P.415

Fig. 2.

2. *Isolated Smooth Muscle*.—Using the isolated rabbit ileum in oxygenated Ringer-Locke solution, we have been able to show that the addition of the active principle to the bath will produce relaxation, as indicated by a diminution in the tonus of the preparation. Neither the rate nor the amplitude of contractions is materially altered, but a reversible inhibition of tonus is demonstrable when 5 units are added to a 50 c.c. bath. Removing the active principle from the bath immediately causes restoration of normal tonus (Fig. 3).

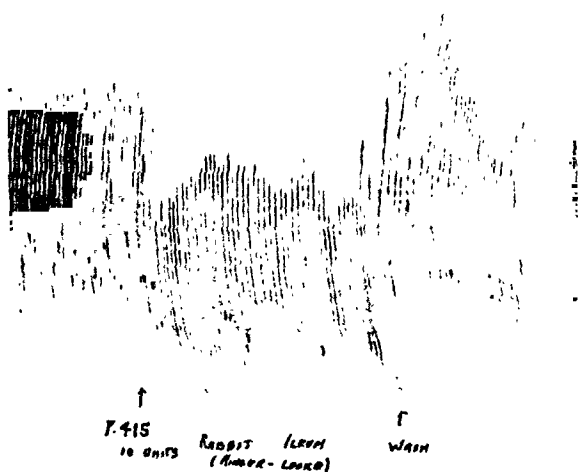


Fig. 3.

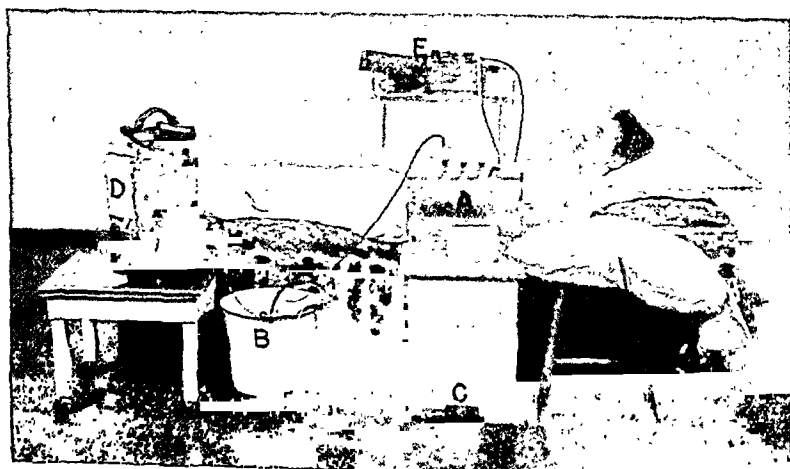


Fig. 4.—A, Water jacketed plethysmograph; B, constant temperature bath; C, circulating pump; D, photoelectric recording unit; E, potentiometric temperature recording equipment.

APPARATUS FOR STUDIES ON MAN

The plethysmograph (Fig. 4) is a modification of that described by Freeman¹⁴ and by Abramson and his colleagues.¹⁵ It consists of a water-jacketed chamber, open at one end. The open end is sealed with a latex rubber membrane, the central

portion of which is made of the cuff of a surgical rubber glove. The forearm is introduced into the chamber through the rubber cuff, and the hand rests on a specially designed sponge rubber support within the chamber. The cuff of the glove fits snugly about the skin of the forearm at the junction of its middle and distal thirds, forming an air-tight seal. A heavy cardboard gasket, cut to conform to the forearm, is fitted over the outer surface of the membrane. This gasket is kept in place by two shaped sheets of metal which are fastened to the outer aspect of the chamber. Three additional openings into the chamber allow for (1) a rubber hose connection to the recording equipment, (2) a calibrating burette, and (3) a thermometer. Water at 32° C. from a constant temperature bath is circulated through the outer jacket by means of a small, heavy-duty pump.

The recording device, which was described by Martin, Marcellus, and Sykowski,¹⁶ consists essentially of a small rubber diaphragm which transmits volume changes from the chamber to a small mirror, hinged on its longitudinal axis. A beam of light plays on the mirror and is reflected into one of two photosensitive cells. These photosensitive cells, in turn, activate a moving pen which records on a calibrated strip of paper moved by a synchronous motor.

Skin temperature records were made by means of a specially designed chromel-nichron thermocouple* which had an area of 0.25 cm.² and a sensitivity of 0.200 to 0.212 millivolts per degree Fahrenheit, in the temperature range in which we were interested (Fig. 4).

All skin temperatures were taken immediately proximal to the nail bed on the dorsum of the fourth finger. "Cold" responses were elicited by placing the hand in water at 5° C. for a period of thirty seconds.

3. Normal Human Controls.—Sixteen persons were examined. These included ten laboratory workers and six patients who were convalescing from acute infectious diseases. The subject was placed in a comfortable supine position and the forearm adjusted in the plethysmograph. After an interval of thirty minutes, which allowed for the establishment of basal conditions, and during which time the instruments were calibrated, the record was started. Skin temperature readings were taken at periodic intervals throughout the course of the entire experiment.

Normal or spontaneous volume fluctuations, such as those described by Abramson and Katzenstein,¹⁷ caused by spontaneous alterations in the caliber of the venous bed, occurred in a few isolated instances. Usually there were a primary rhythmicity associated with respiratory movements and a superimposed secondary rhythm which showed volume fluctuations of the same order as those observed during the respiratory cycle. The application of the standardized cold stimulus gave rise to an immediate diminution in hand volume; the latter returned to its base level within three minutes after the stimulus was withdrawn. Fig. 6 shows a typical cold-pressor response; the diminution in hand volume of 5 c.c. is indicated by a rise of the writing point, and the subsequent, prompt return of hand volume to its original level is shown by a fall. The intramuscular administration of physiologic saline solution or of

*Six chromel-nichron junctions, arranged in series. This was designed and built for us by the General Engineering Laboratories, General Electric Company, Schenectady, N. Y.

liver extract produced a similar diminution in hand volume in approximately 20 per cent of this normal group. This we attributed to psychogenic factors resulting from the introduction of a hypodermic needle into hypersensitive persons. In the majority of the subjects the administration of the saline or liver extract gave rise to no peripheral volume change. In no instance did the administration of a placebo give rise to an increase in limb volume or any alteration in the intensity of the response to the standard cold stimulus.

The intramuscular administration of 10 units of the active pancreatic extract in 1.0 c.c. of physiologic saline solution rarely elicits any local reaction. Those persons who showed a transient diminution in limb volume after the administration of saline or liver extract usually showed the same diminution after the injection of the active principle. All normal subjects ultimately showed a marked increase in limb volume, associated with an elevation of skin temperature, after the injection of such doses. The maximal effect was reached within fifteen minutes of administration and continued throughout the entire period of observation (ca. two hours). The average volume increase was 12 c.c., and the average temperature elevation, 5° F. More striking than the increase in limb volume was the modification of the response to the cold stimulus. In 68 per cent of this normal group the response to the cold stimulus was entirely abolished, whereas the remainder showed a marked diminution in the intensity and duration of the response. These results are illustrated graphically in Fig. 5, which shows the mean response to the cold stimulus before and after the administration of the active principle.

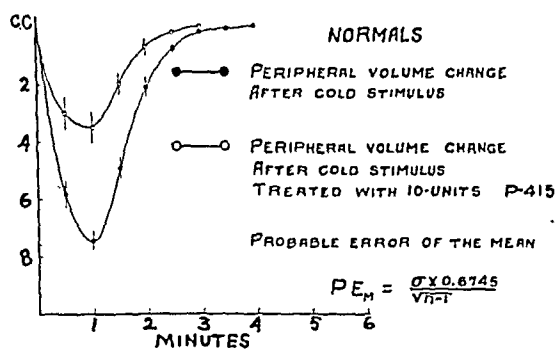
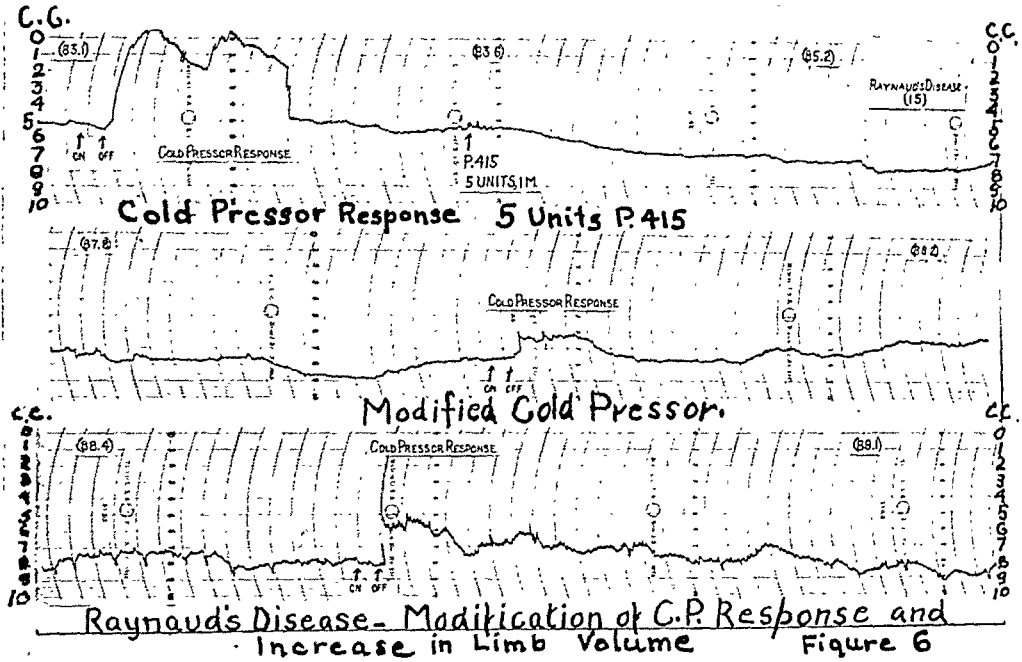


Fig. 5.

4. *Peripheral Arterial Disease.*—A series of twenty-one patients with established or suspected peripheral arterial disease were examined and treated with the active principle according to the scheme outlined above. These included cases of established Raynaud's disease, Buerger's disease, arteriosclerosis with hypertension, thrombophlebitis, and scleroderma. The majority of those who comprised this group differed from the normal subjects in so far as their response to the standard cold stimulus was concerned. As was pointed out above, the normal persons

required approximately three minutes after the withdrawal of the cold stimulus for the re-establishment of the basal volume level. This group required more than ten minutes for the re-establishment of this level.



spasticity may be encountered also in Buerger's disease, even though the primary lesion is an obliterative angiitis, and it may be an added factor in the symptomatology of the disease. We have not seen the spastic type of response in hypertensive arteriosclerotic patients, but have encountered it in cases of thrombophlebitis and scleroderma. We have also found it in three cases which could not be fitted into any clearly delineated clinical entity, but the patients' clinical manifestations were sufficiently suggestive of peripheral arterial disease to warrant serious consideration of this possibility (Cases 5, 9, 11).

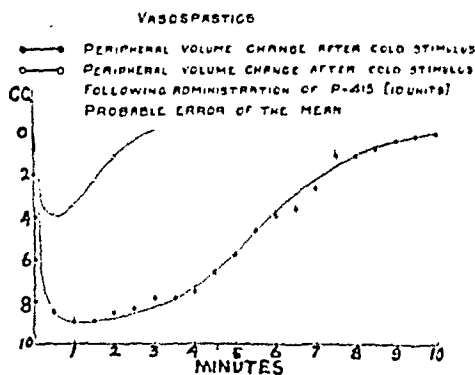


Fig. 8.

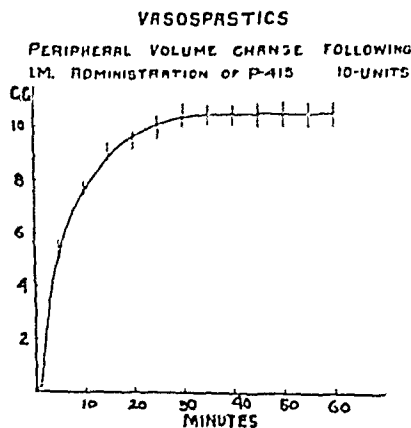


Fig. 9.

The spastic type of response was modified by the administration of 10 units of the active principle, so that it approximated the response of the normal person after medication (Fig. 6). This was associated with an increase in limb volume, elevation of the skin temperature, and, in most instances, symptomatic relief. Such persons, when given a placebo (intramuscular injection of 15 U.S.P. units of liver extract), failed to show any of the changes enumerated above (Fig. 7). The mean values for the cold-pressor response in this group of patients have been ascertained, and are shown in graphic form in Fig. 8. The conversion of this spastic type of volume change to the normal pattern after

the intramuscular administration of 10 units of the active principle is also recorded.

With the exception of the two patients with hypertension and arteriosclerosis and one with Buerger's disease, the entire group showed increased peripheral volume and an elevation of the skin temperature. The maximal effect appeared about fifteen minutes after medication and persisted throughout the entire period of observation. Symptomatic relief lasted from twenty-four to seventy-two hours (Fig. 9).

The details of our observations on a series of patients with peripheral vascular disease are presented.

Case 1.—Miss H. O., aged 30 years. Raynaud's disease.

Thoracic preganglionic (T-2, 3) sympathectomy performed six months prior to examination because of gangrenous changes in the finger tips, followed by improvement.

No vasoconstriction as a result of the application of cold. Ten units of tissue extract produced a slight elevation of skin temperature (2° F.) and slight peripheral vasodilatation (6 c.c.). No peripheral vasodilatation or elevation of skin temperature resulted from the administration of a saline placebo. There has been no return of symptoms. This patient was apparently completely cured by surgical measures.

Case 2.—Mrs. J. M., aged 54 years. Raynaud's disease.

Classical Raynaud's symptom complex which had persisted for fifteen years and had shown marked exacerbation during the preceding two years. Pain of a sharp, lancinating character, in addition to a dull ache.

Spastic response to cold stimulation. Ten units of tissue extract produced a 6° F. elevation of skin temperature and marked (12 c.c.) peripheral vasodilatation. This was associated with immediate symptomatic relief.

Subsequent medication with a saline placebo produced no vasodilatation, no elevation of skin temperature, and no symptomatic relief.

Twenty units of tissue extract produced symptomatic relief for 48 to 72 hours. Patient has been symptom-free for six months.

Case 3.—Miss S. P., aged 18 years. Early Raynaud's disease.

Complained of pain in hands and forearms of three years' duration, brought on by exposure to cold; pain was associated with color changes.

Plethysmographic examination showed spastic reaction to cold stimulation. The administration of 10 units of tissue extract abolished the spastic reaction and was associated with a 4° F. elevation in skin temperature and peripheral vasodilatation (10 c.c.). Complete symptomatic relief.

Subsequent examination showed no change, no vasospasticity, no elevation in skin temperature, and no peripheral vasodilatation after the administration of a placebo (liver extract).

Patient received 10-unit doses of tissue extract at three-day intervals, and this controlled the symptoms. She became free of symptoms with the advent of warmer weather, and treatment was discontinued.

Case 4.—Mrs. A. H. S., aged 64 years. Raynaud's disease.

Characteristic symptom complex, including bilateral pain and color changes in hands and feet after exposure to cold. Symptoms had persisted for twenty-five years and had become markedly worse in the preceding two years.

Plethysmographic examination showed characteristic spastic reaction to cold, which was abolished by the administration of 10 units of tissue extract. This was

associated with a 6° F. elevation in skin temperature and marked peripheral vasodilatation (12 c.c.). There was also complete symptomatic relief which persisted for forty-eight hours.

Subsequent administration of a placebo produced neither subjective nor objective changes.

At the present time the patient receives one dose of 20 units per week, which has maintained symptomatic relief for a period of six months.

Case 5.—Miss J. R., aged 21 years. Early Raynaud's disease (?).

Complained of shooting pain in the right hand, with spread to the shoulder. This was precipitated by exposure to cold and was not associated with color changes.

Plethysmographic examination showed a slight spastic reaction. The administration of 10 units of tissue extract abolished the spastic response, and produced a 6° F. elevation of skin temperature and definite (10 c.c.) peripheral vasodilatation. There was complete subjective relief for a period of twenty-four hours.

Subsequent administration of a placebo produced no objective changes, but was followed by complete symptomatic relief which persisted for approximately twenty-four hours.

Treatment was discontinued.

Case 6.—Miss J. Van A., aged 27 years. Raynaud's disease (?).

Complained of pain in the right hand and forearm, of two years' duration, precipitated by cold. No color changes. Markedly spastic type of response to exposure to cold; the injection of 10 units of tissue extract abolished the spastic response and produced a 6° F. elevation of skin temperature and marked peripheral vasodilatation (12 c.c.). There was partial symptomatic relief.

The administration of a placebo produced no objective changes, but gave symptomatic relief.

Patient was not followed.

Case 7.—Mrs. K. S., aged 40 years. Raynaud's disease.

Classical picture, with pain, color changes, and pregangrenous trophic changes about the finger tips. Pronounced spastic response to cold which was abolished by the administration of 10 units of tissue extract. This was associated with marked peripheral vasodilatation (16 c.c.) and elevation of skin temperature (4° F.). There was complete symptomatic relief for forty-eight hours.

The administration of a placebo produced no objective changes or symptomatic relief.

Six months later the patient was receiving approximately 40 units per week in divided doses and was symptom-free.

Case 8.—Mr. J. B., aged 51 years. Buerger's disease.

Thromboangiitis obliterans demonstrated histologically. Mid-thigh amputation of left leg for gangrenous change of left foot performed eight months earlier. At the same time, the distal phalanges of the fourth and fifth fingers of the left hand and fifth finger of the right hand were amputated.

Patient had a foul-smelling, discharging ulcer on the internal malleolus of the right foot. This was surrounded by a cyanotic, edematous zone, and the edema involved the entire lower third of the leg.

Plethysmographic examination showed a markedly spastic response to cold stimulation; this was abolished by the administration of 10 units of the tissue extract; and, in addition, an elevation of the skin temperature (7° F.), marked peripheral vasodilatation (18 c.c.), and complete relief of symptoms occurred.

The administration of a placebo produced no objective changes and had no influence on the symptoms.

The intramuscular injection of tissue extract at 48-hour intervals (20 units) resulted in complete symptomatic relief and marked improvement in the condition of the ulcer. By the end of the third week the cyanosis and edema had disappeared, and the ulcer presented a clean, granulating surface. No adjuvant therapy was employed in this case, and objective, as well as subjective, improvement occurred without rest in bed.

Case 9.—Mr. J. G., aged 51 years. Buerger's disease (?).

Pain in the left leg of two years' duration. Brawny swelling involving the foot, the ankle, and the lower portion of the leg, with an area of exquisite tenderness over the femoral vein in the inguinal region. The popliteal, posterior tibial, and dorsalis pedis pulses on the left could not be palpated. No history of diabetes, hypertension, or syphilis.

Plethysmographic examination showed a markedly spastic response to cold stimulation which disappeared after the administration of 10 units of the tissue extract. This was associated with a slight (4° F.) elevation of skin temperature and slight (5 c.c.) peripheral vasodilatation. There was no symptomatic relief.

No objective or subjective changes were produced by the administration of a placebo. Patient was not followed.

Case 10.—Mr. J. B., aged 53 years. Buerger's disease.

Symptoms had been present for twenty-four years. During the preceding two years, trophic ulcers developed between the toes of the right foot and did not respond to medication. The popliteal and dorsalis pedis pulses could barely be felt. Exposure to cold produced a typical spastic response which was abolished by the administration of 10 units of tissue extract.

This was associated with a 6° F. elevation of skin temperature, marked peripheral vasodilatation (13 c.c.), and complete symptomatic relief.

No objective or subjective changes occurred after the administration of a placebo.

Six months after the beginning of treatment the patient was symptom-free on 30 to 60 units of tissue extract per week, and the trophic ulcers had disappeared.

Case 11.—Mr. J. O., aged 55 years. Buerger's disease (?).

Patient complained of intermittent claudication of the right leg, with a constant, gnawing pain in both feet, of three years' duration. Twelve years before, after exposure to intense cold, the first and second toes of the right foot were frostbitten, and amputation was performed. There was no history of hypertension or other chronic disease.

The dorsalis pedis and popliteal pulses could not be palpated on the right. He gave a spastic response to cold stimulation which was abolished by the administration of 10 units of tissue extract. This was associated with a slight (3° F.) elevation of skin temperature and slight (7 c.c.) peripheral vasodilatation. There was partial symptomatic relief.

Three weeks after the original examination the patient responded normally to cold stimulation, and the administration of a tissue extract had no significant objective or subjective effect. Subsequently there was progression of the peripheral arterial lesions.

Case 12.—Mr. J. A., aged 35 years. Buerger's disease.

Thromboangiitis obliterans demonstrated histologically. Four weeks prior to examination, mid-thigh amputation was performed because of gangrenous changes in the left foot. The amputation stump was healing poorly, and pain and trophic changes appeared in the other foot.

Plethysmographic examination showed a markedly spastic reaction to cold stimulation which was abolished by the administration of 10 units of tissue extract.

This was associated with a marked (8° F.) elevation of skin temperature, an increase in peripheral volume (16 c.c.), and complete symptomatic relief.

The patient received 10 units of the extract daily during the three-week period of hospitalization, and was free from symptoms. The amputation stump healed rapidly.

Case 13.—Mr. F. M., aged 48 years. Buerger's disease.

Thromboangiitis obliterans demonstrated histologically. Symptoms persisted for three years. Fifteen months before, mid-thigh amputation was performed because of gangrenous changes in the right foot. He complained of intermittent claudication on the left side, the nail beds were cyanotic, and trophic changes were present. The dorsalis pedis pulse could be palpated with difficulty.

Examination showed a normal response to cold stimulation which was not affected by the administration of 10 units of the tissue extract. There were no objective changes.

Subsequently, the administration of 30 units of the tissue extract failed to alter the peripheral circulation or to affect the symptoms.

Case 14.—Mr. M. T., aged 49 years. Buerger's disease.

Intermittent claudication and trophic changes in the left foot for a period of eight months. Both popliteal pulses were palpable, but the dorsalis pedis and posterior tibial on the left were not.

Examination showed a markedly spastic response to cold stimulation which could be abolished by the administration of 10 units of tissue extract. This was associated with an elevation (8° F.) of skin temperature, peripheral vasodilatation (12 c.c.), and symptomatic relief.

Subsequent examination showed neither objective nor subjective changes after the administration of a placebo. The patient was given 40 units of tissue extract per week, which kept him asymptomatic for three weeks, or until the arrival of warm weather.

Case 15.—Mr. J. G., aged 56 years. Arteriosclerosis with claudication.

Complained of a "dead feeling" and pain in both legs for a period of two years. The patient was a diabetic, but the disease was kept under control without insulin.

He gave a spastic response to cold stimulation, which was abolished by the administration of 10 units of tissue extract. This was associated with a 4° F. elevation of skin temperature and slight (6 c.c.) peripheral vasodilatation. The patient remained symptom-free for twenty-four hours.

A placebo produced neither subjective nor objective changes.

The subsequent administration of 10 to 30 units of tissue extract gave varying results; at times symptomatic relief was obtained, and, at other times, there was no effect. Treatment was discontinued.

Case 16.—Mrs. H. W., aged 47 years. Arteriosclerosis, marked hypertension with arteriosclerotic changes, diabetes, and nephrosclerosis.

Complained of pain in both legs on exertion. Normal response to cold stimulation. The administration of 20 units of tissue extract produced no demonstrable effect on symptoms, skin temperature, or limb volume.

Case 17.—Mr. J. B., aged 50 years. Arteriosclerosis, hypertension with marked arteriosclerotic changes.

Complained of pain on exercising and a persistent, nonhealing trophic ulcer on the shin.

Plethysmographic examination showed a normal response to cold stimulation. The administration of 20 units of tissue extract produced no subjective or objective changes.

Case 18.—Mrs. D. Z., aged 66 years. Scleroderma.

Marked scleroderma, verified by biopsy.

Plethysmographic examination showed a markedly spastic response to cold stimulation which was abolished by the intramuscular administration of 10 units of tissue extract; this was associated with slight peripheral dilatation (7 c.c.) and partial symptomatic relief. Skin temperature was not recorded.

Subsequently, the administration of 10 units per day gave the patient considerable symptomatic relief.

Case 19.—Mrs. L. D., aged 69 years. Thrombophlebitis.

Acute thrombophlebitis involving femoral vein. The right leg was swollen, brawny, and exquisitely tender.

There was a markedly spastic response to cold stimulation which was abolished by the administration of 10 units of tissue extract. Slight (6 c.c.) peripheral vasodilatation was associated with questionable symptomatic relief. Skin temperature was not recorded.

Case 20.—Mr. L. P., aged 33 years. Orthopedic disorder (foot strain).

Complained of acute pain in the feet, extending from the soles up to the calves. The pain bore no relation to environmental temperature; it occurred when the patient stood in one place for any length of time. The pain could be relieved by active or passive exercises.

No signs of organic arterial disease. Normal response to cold stimulation. The administration of 10 units of tissue extract produced a slight (2° F.) elevation of skin temperature, slight (8 c.c.) peripheral vasodilatation, and no effect on the symptoms.

Case 21.—Mrs. F. G., aged 37 years. Thrombophlebitis.

Acute thrombophlebitis eighteen months prior to examination. Trophic ulcer on the shin of the left leg. Patient complained of pain on exercise.

Normal response to cold stimulation. The administration of 10 units of tissue extract produced a slight (1° F.) elevation of skin temperature and slight (6 c.c.) peripheral vasodilatation. There was no effect upon the symptoms.

SUMMARY

Table I summarizes the results of treatment with the extract in the twenty-one cases of peripheral arterial disease. It will be noted that there were fifteen instances in which the response to cold was of the spastic type. These patients reacted especially well to the extract; all of them showed significant increases in limb volume and rises in skin temperature. Symptomatic relief was complete in eight cases and partial in four. The three patients in the "spastic group" who failed to benefit symptomatically from administration of the extract had Buerger's disease (Cases 9 and 11) or thrombophlebitis (Case 19). Six patients in the series of twenty-one subjects gave a normal response to cold stimulation, i.e., they showed no evidence of vasospasm. None of these patients received any benefit from injections of the pancreatic extract. In Case 1 the patient's Raynaud's disease was asymptomatic as a result of preganglionic sympathectomy. The operation had evidently completely abolished the abnormal response to cold. Case 13 was one of advanced Buerger's disease, Cases 16 and 17 were examples of arteriosclerosis, Case 20 was one of foot strain with no peripheral vascular disease, and Case 21 was one of thrombophlebitis with ulceration.

TABLE I

CASE	UNTREATED				EFFECT OF TREATMENT WITH P-415 (10 UNITS, I.M.)				
	DIAGNOSIS	COLD NORMAL	STIMULUS SPASTIC	COLD NORMAL	STIMULUS SPASTIC	SKIN TEMP.	VASODILA- TATION	SYMPTOMS (RELIEF)	
1	Raynaud's Dis.	Nil	++	Nil		+2° F.	+ 6 c.c.	Nil	
2	Raynaud's Dis.		++			+6° F.	+12 c.c.	Complete	
3	Raynaud's Dis.		++			+4° F.	+10 c.c.	Complete	
4	Raynaud's Dis.		++			+6° F.	+12 c.c.	Complete	
5	Raynaud's Dis. (?)		++			+6° F.	+10 c.c.	24 hr. inconstant	
6	Raynaud's Dis. (?)		++			+6° F.	+12 c.c.	Partial, not followed	
7	Raynaud's Dis.		+++			+6° F.	+16 c.c.	Complete	
8	Raynaud's Dis.		+++			+7° F.	+18 c.c.	Complete	
9	Buerger's Dis. (?)	x	++	x		+4° F.	+ 5 c.c.	None	
10	Buerger's Dis.		++			+6° F.	+13 c.c.	Complete	
11	Buerger's Dis. (?)		++			+3° F.	+ 7 c.c.	None	
12	Buerger's Dis.		++			+8° F.	+16 c.c.	Complete	
13	Buerger's Dis.		+++			+0° F.	+ 0 c.c.	None	
14	Buerger's Dis.		+++			+8° F.	+12 c.c.	24 hr. complete	
15	Arteriosclerosis with Claudication		+++			+4° F.	+ 6 c.c.	Partial, inconstant	
16	Arteriosclerosis					No chg.	No chg.	None	
17	Arteriosclerosis					No chg.	No chg.	None	
18	Scleroderma		+++			Not re- corded	+ 7 c.c.	Partial	
19	Thrombophlebitis	x	+++	x		Not re- corded	+ 6 c.c.	Questionable	
20	Orthopedic Disorder (Foot Strain)					+2° F.	+ 8 c.c.	None	
21	Thrombophlebitis with Ulceration					+1° F.	+ 6 c.c.	None	

CONCLUSIONS

We have presented objective proof of the physiologic activity of a new and potent pancreatic extract. When used on animals and on normal human controls it has been shown to cause peripheral vasodilatation in the limbs, as measured by an increase in volume and a rise in temperature. This extract has a most beneficial symptomatic effect upon nearly all patients with peripheral vascular disease when vasospasm is a prominent feature. Relief has been obtained for periods of one to six months with administration at intervals of two to seven days.



Fig. 10.

ADDENDUM

Since this investigation was completed we have had the opportunity of studying and treating a most unusual patient. Miss G. B., aged 31, hospital number 96038, was admitted to the Albany Hospital May 31, 1942. She gave a history of long-standing Raynaud's disease, with marked ulceration over the feet and ankles, as shown in Fig. 10. Twelve years previously she had a lumbar sympathectomy at another clinic,

with temporary relief of pain for about two years. For the preceding two years she had been bedridden, and dependent on narcotics for relief of pain. With the plethysmographic technique it was found that the patient showed marked vasospasm. The immediate response to tissue extract was feeble, and very little hope of clinical improvement was entertained. However, with doses of 20 units twice a week, plus the use

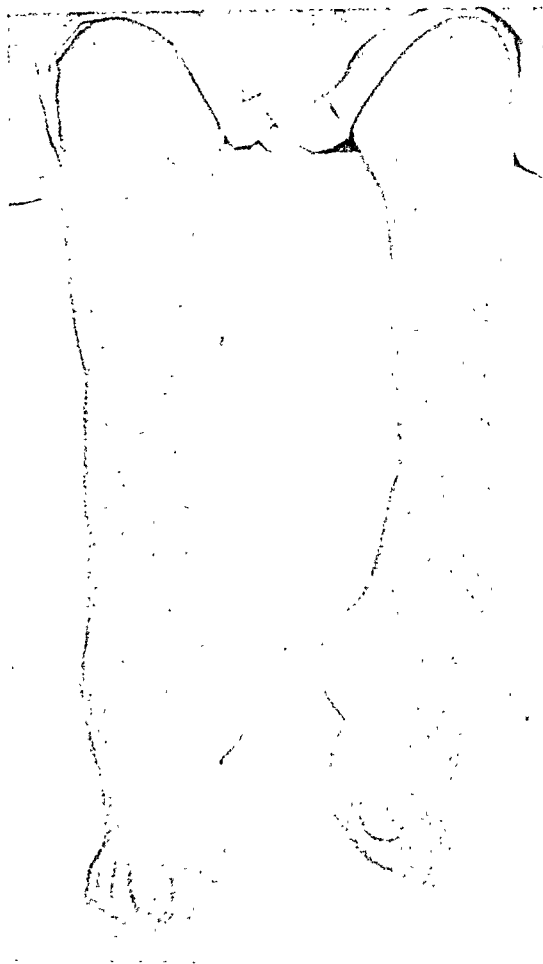


Fig. 11.

of sulfanilamide-sulfathiazole powder, a dramatic response was obtained. The pain had disappeared at the end of two weeks, and healing had begun. By October 17 healing was complete, as shown in Fig. 11.

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PERICARDIAL EFFUSION IN MYXEDEMA

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EFFUSION into the pericardium and other serous cavities is a complication of myxedema on which few data are available. Zondek¹ first described myxedema heart disease as a clinical entity, and Gordon² first proved that pericardial effusion might account for at least part of the apparent cardiac enlargement. The occurrence of serous effusions was noted at autopsy in cases of myxedema as early as 1888.³ Tatum⁴ and Goldberg⁵ reproduced pericardial effusion in thyroidectomized sheep and goats. Freeman⁶ reported the first thoroughly described case of massive pericardial effusion in myxedema. Since his report, other instances have been recorded.^{7, 8} Although the case described by Merrill⁹ resembled myxedema clinically, the basal metabolic rate was elevated. In the case reported by Carns and Lee,¹⁰ the presence of pericardial fluid was not demonstrated by aspiration. Two patients with untreated myxedema who came to autopsy at the Massachusetts General Hospital had pericardial effusion, although one was small in amount.¹¹ Often the picture is complicated by the development of arteriosclerosis, especially in the coronary arteries, if the myxedema remains untreated for a period of years.

The following two cases, in both of which there was underlying arteriosclerotic heart disease, add a few data, including the first quantitative studies on the cholesterol content of the pericardial fluid, and are interesting because of the variation in response to the administration of thyroid substance.

CASE 1.—A 53-year-old, white, farm housewife, was admitted to Duke Hospital October 1, 1938, complaining of weakness, intermittent swelling of the abdomen, and slight dyspnea, of eighteen months' duration. The feet were always cold.

The patient was pale, undernourished, breathing quietly, and not orthopneic. Speech was slow and the voice was hoarse. The tongue showed no papillary atrophy. The skin was dry and thickened. The breath sounds at the bases of the lungs were distant. The heart was enlarged, the precordium quiet, the rate slow, and the sounds distant; the blood pressure was 120/80. The abdomen was rounded, shifting dullness was present, and the liver extended 8 cm. below the costal margin. Pitting edema was present over the sacrum, but not over the legs.

The hemoglobin was 10.9 Gm., the erythrocytes numbered 2,600,000, the color index was 1.3, and the mean corpuscular volume was 140 cubic micra. The urine contained no albumin. Gastric analysis showed 64 degrees of free HCl after the injection of histamine. The total serum protein was 6.4 per cent, with albumin 3.6 per cent, and globulin 2.8 per cent; the cholesterol was 330 mg. per cent. The basal metabolic

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rate was minus 31 per cent. The oral glucose tolerance test revealed a flat curve. Fluoroscopic examination indicated pericardial and bilateral pleural effusion (Fig. 1).

On the fourth hospital day, fluid was removed from the peritoneal and pleural cavities for diagnosis; 125 c.c. were removed from the pericardium, and 25 c.c. of air were injected. After this the venous pressure fell from 300 to 135 mm. of water, the electrocardiogram showed an increase in voltage, and the blood pressure rose to 130/80, but no subjective improvement was noted. After one day on 64 mg. of desiccated thyroid gland, without diuretics or digitalis, a dramatic diuresis began, reaching a peak of 2,300 c.c. after four days of treatment with the same dose; the free fluid soon disappeared from the serous cavities. The total protein content of the pericardial fluid was 4.9 per cent, of the pleural fluid, 2.9 per cent, and of the peritoneal fluid, 2.4 per cent.

The patient took desiccated thyroid irregularly until April, 1941, when nicotinic acid tablets were substituted. She was readmitted May 14, 1941, at which time she

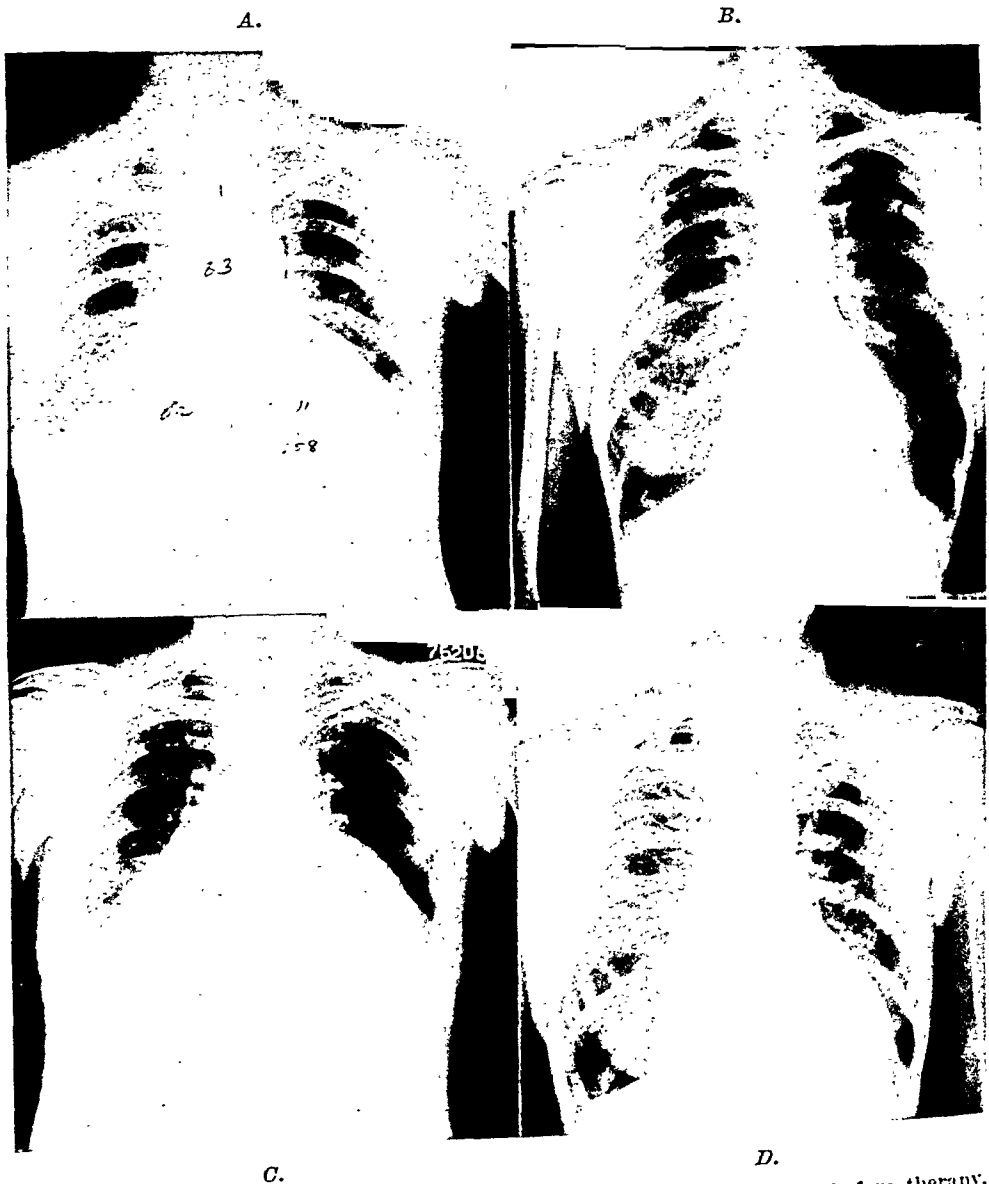


Fig. 1.—Case 1. A, Massive pericardial and small pleural effusion, before therapy. B, Complete disappearance of effusions on thyroid therapy alone. C, Recurrence of effusions after withdrawal of thyroid. D, Improvement a second time on thyroid therapy, after failure to improve on digitalis.

was orthopneic, and had physical and roentgenologic evidence of fluid in all the serous cavities (Fig. 2), peripheral edema, and signs of myxedema. The hemoglobin was 13 Gm., the erythrocytes numbered 4,400,000, the color index was 0.95, the mean corpuscular volume, 97.7 cubic micra, the basal metabolic rate, minus 35 per cent, the vital capacity, 600 c.c., the venous pressure, 190 mm. of water, and the serum cholesterol, 270 mg. per cent; the serum proteins were 5.0 per cent, with albumin 2.7 per cent and globulin 2.3 per cent, and the circulation time was 19 seconds by the calcium gluconate method. The urine contained no albumin. The pericardial fluid contained 4.3 per cent of total protein and 92 mg. per cent of cholesterol.



Fig. 2.—Case 1. A, Roentgenkymograph when patient was on irregular doses of thyroid, showing absence of pulsations over the lower third of the heart and good pulsations over the great vessels, indicating recurrence of small pericardial effusion without impairment of ventricular contraction. B, Recurrence of massive pericardial and small pleural effusion after complete withdrawal of thyroid therapy; the small pulsations over the great vessels indicate feeble ventricular contractions.

After rest in bed, restriction of fluids, and complete digitalization produced no response, 64 mg. of thyroid substance were administered daily, with a marked diuresis of 2,700 c.c. on the second day and a weight loss of 3 kg. in two days. On the eleventh and sixteenth days the thyroid dosage was increased, with the result that there was a second and third diuresis, each lasting three days. The edema, serous effusions, mental sluggishness, and coolness and thickening of the skin disappeared.

CASE 2.—A 62-year-old white farmer was admitted to the Duke Hospital September 11, 1939, complaining of orthopnea and edema of one month's duration. He had been seen in 1932, 1934, and 1937, when he had pellagra, anemia, and hypothyroidism, and had always responded promptly to therapy with desiccated thyroid, iron, and yeast.

The patient presented the classic appearance of myxedema. Signs of fluid were present at the bases of both lungs. The supracardiac dullness was greatly increased (Fig. 3), and the heart sounds were barely audible; the blood pressure was 168/114. The abdomen was distended and tympanitic, and the liver was enlarged. Pitting edema was present below the knees. The skin over the hands and feet was rough, dry, red, and scaling.

The hemoglobin was 9 Gm., the erythrocytes numbered 3,100,000, the basal metabolic rate was minus 39 per cent, the serum proteins were 6.4 per cent, with

albumin 3.3 per cent and globulin 3.1 per cent, and the cholesterol was 155 mg. per cent. The urine contained a small amount (1+) of albumin. Fluid aspirated from the pericardium contained 5.7 per cent of protein, but also 9,000 erythrocytes per c.mm., probably as the result of trauma. After receiving 100 mg. of thiamin chloride daily, intravenously, for four days without diuresis, the administration of thyroid substance was started, but the expected improvement did not occur. After subsequent digitalization, the edema and pleural and pericardial effusion disappeared, but some evidence of ascites remained.

At home he discontinued medication, and returned in October, 1940, with classic myxedema, but with serous effusion only in the right pleural sac. The skin lesions of pellagra had recurred.

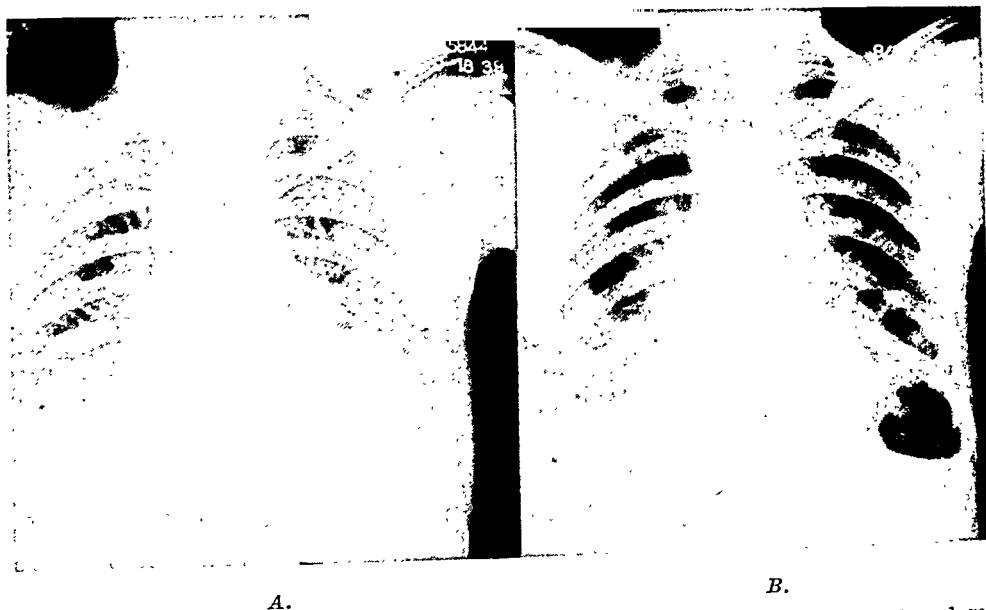


Fig. 3.—Case 2. A, Pericardial effusion after partial aspiration of fluid and replacement with air, before thyroid administration and after failure of vitamin therapy. B, Small recurrent pleural effusion on right after thyroid therapy was discontinued, and clinical signs of myxedema had returned.

The hemoglobin was 9.5 Gm., the erythrocytes numbered 2,450,000, the color index was 1.2, the mean corpuscular volume, 98 cubic micra, and the basal metabolic rate, minus 34 per cent. The urine contained no albumin.

The pellagra responded promptly to nicotinic acid, and the myxedema, to thyroid substance. He received no digitalis.

DISCUSSION

Of these two instances of pericardial effusion in association with myxedema, the first was undoubtedly caused by the myxedema itself, for the fluid disappeared under thyroid replacement therapy, recurred after complete withdrawal of thyroid, did not disappear under digitalis therapy, and did respond a second time to thyroid administration. The effusion in the second case did not respond to thyroid substance alone, but also required digitalis, and did not recur on withdrawal of thyroid and digitalis. In each of these cases there was evidence of underlying arteriosclerotic heart disease. The more severely damaged heart (Case 2) did not respond to thyroid substance alone, and the second response in

TABLE I

AGE	SEX	DURATION	B. M. R. %	URINE ALBUMIN	BLOOD				PERICARDIAL FLUID							TOTAL PROT. %	CHOLEST. MG. %		
					TOTAL PRO- TEIN %	ALB. %	GLOB. %	CHOLEST. MG. %	CULTURE	G.P.*	W.B.C.	P.M.N. %	LYMPH. %	MON. %	SP. GR.				
682	M		-42							Neg.									
396	M	6 yr.	-45	Trace					Neg.	Neg.			50	12	38	1.019	4.5		
349	F	3 yr.	+19	Trace					Contam- inated	Neg.	75			100		1.020			Cry-stals
487	F	10 yr. 15 yr.	-70	Neg.	6.4	3.8	2.6	357	Neg.	Neg.	100	2600		99		1.022	5.0		
5	F	3 yr.	-45	Trace				236	Neg.							1.020	3.2		
5410	F	3 mo.	-28	Neg.				227											
53	F	1 1/2 yr. 4 yr.	-31 -35	Neg. Neg.	6.4 5.0	3.6 2.7	2.8 2.3	319 270	Neg.		72 109		56	100 34	10	1.015	4.9 4.3	92	
62	M	7 yr. 8 yr.	-39 -34	1+ Neg.	6.4 6.5	3.3 2.4	3.1 4.1	455 292	Neg.							1.020	5.7		

*Guinea pig inoculation.

the case of the less severely damaged heart (Case 1) was not so dramatic as the first. The amount of thyroid required to produce diuresis was small, which has been noted before. The possibility of beriberi heart disease in the second case was ruled out by a trial on adequate doses of thiamin; although no unquestioned instance of beriberi heart disease has ever been recognized in this clinic, the simultaneous occurrence of another vitamin deficiency state—pellagra—which is a rare happening, according to Greene,¹² made this conceivable.

Other interesting features presented by these cases, and probably related to associated deficiency states, were the hyperchromic, macrocytic anemia, with free gastric HCl after histamine stimulation, and the low glucose tolerance curve which quickly became normal with thyroid therapy. Delayed relaxation of the tendon reflexes, first observed in myxedema by Chaney, was observed.¹³

The cholesterol content of the pericardial fluid was very much less than that recorded in a case of tuberculous "cholesterol pericarditis."¹⁴ No data on this point could be found in other cases of myxedema. In our case the level was much lower than that of the blood. The protein content of the fluid was similar to that observed by others, and was uniformly less than that of the blood serum. No explanation has ever been offered for the presence of leucocytes, often polymorphonuclears, in the pericardial fluid. The fluids have been sterile on culture and guinea pig inoculation, except in the case of Merrill,⁹ in which contamination was suspected.

The absence of more than a trace of albumin in the urine would indicate that, if cardiac failure, *per se*, were responsible for the effusion, it was of such minor degree that renal engorgement was not present; this might be a helpful differential point.

The electrocardiograms showed an increase in voltage after the administration of thyroid substance; no changes were noted which would indicate the presence or absence of pericardial fluid.

The roentgenkymograms in Case 1 (Fig. 2) showed absence of pulsations over the lower third of the heart, with good pulsations over the great vessels; they indicated no impairment of ventricular contraction, even though pericardial effusion was developing after incomplete withdrawal of thyroid therapy. The pulsations over the great vessels were greatly reduced after complete withdrawal of thyroid therapy and the development of massive pericardial effusion. Study of additional cases of myxedema heart by means of the roentgenkymograph, and perhaps other methods, may produce evidence that muscular relaxation is impaired in the ventricle as well as in skeletal muscle.

SUMMARY

Pericardial effusion is a rare complication of myxedema heart disease. The factors responsible are unknown, but myocardial failure is thought to be a minor one. The laboratory data in cases of pericardial effusion

associated with myxedema have been tabulated. The protein and cholesterol contents of the pericardial fluid are less than those of the blood. No adequate explanation has been offered for the occasional presence of leucocytes, especially polymorphonuclear leucocytes, in the fluid.

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AORTIC ANEURYSM WITH RUPTURE INTO THE PULMONARY ARTERY

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ANEURYSMS of the aorta are not uncommon, especially in communities with a large Negro population. Rupture of such an aneurysm into the pulmonary artery, however, is sufficiently unusual and interesting to warrant special attention. It is of further interest that such a rupture is compatible with life for a varying period of time, and, in some instances, as in one of our cases, can be diagnosed ante mortem when there is a peculiar, continuous, "humming-top" murmur. Probably the most recent case report of this disease is that of White, Chamberlain, and Kelson.¹ These authors state that there were about fifty cases on record before 1913, and that there have been about a dozen reports in the last twenty-five years. The survival period in the cases reviewed by these authors ranged from a few hours to four years. Thurman,² Peacock,³ Taylor,⁴ and Kappis⁵ were among the early writers and investigators in this field.

CASE REPORTS

CASE 1.—The patient was a 40-year-old colored woman who came to the hospital July 27, 1941, complaining of palpitation, weakness, swelling of the ankles, and abdominal pain. These complaints began two and one-half months previously. There was also intermittent precordial pain, radiating to the left flank. During the two months previous to admission she complained of attacks of loss of consciousness three or four times daily; these were brought on by exertion, and lasted for approximately fifteen minutes. Vomiting had also been troublesome for a month before admission.

There was no past history suggestive of a primary syphilitic lesion or of anti-syphilitic treatment.

On admission, the patient's temperature was 98.6°, the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 144/40. Physical examination showed obvious respiratory difficulty, pallor of the conjunctivae, and distention of the neck veins. The trachea was in the midline, and no tracheal tug was noted; râles were heard at the bases of both lungs. The heart was enlarged to the sixth intercostal space in the anterior axillary line on the left. A thrill was felt in the second and third intercostal spaces to the left of the sternum. In the pulmonic area and above, a loud, harsh systolic murmur, with a long, low diastolic murmur, was heard. These murmurs together suggested the more or less classical continuous "humming-top" murmur. The pulmonic second sound was somewhat accentuated;

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the pulmonic first sound was obscured by the murmur. There was no detectable increase in the width of sternal dullness at the base of the heart. The liver was palpable on the right below the level of the umbilicus. Fluid was thought to be present in the abdomen. The reflexes were equal and active. There was edema of the feet, legs, and over the sacrum.

The blood cell count was normal. Urinalyses showed a specific gravity which varied between 1.014 and 1.025, and albumin, erythrocytes, leucocytes, and casts. Both the Kline and Kolmer reactions on the blood serum were strongly positive on two occasions. The blood urea varied between 21 and 44.1 mg. per cent. The blood glucose and protein were within normal limits. A phenolsulfonephthalein test of kidney function on Sept. 23, 1941, showed an excretion of only 35 per cent of the dye in two hours. A roentgenogram of the chest on July 27, 1941, showed enlargement of the cardiac shadow and evidence of an aneurysm of the arch of the aorta. On Aug. 8, 1941, diotrast was given intravenously and radiograms taken. The latter showed what appeared to be enlargement of the pulmonary artery. Electrocardiograms indicated the presence of myocardial disease. A cardiac sound tracing on Aug. 7, 1941, showed a systolic murmur which was loudest at the base, and also a diastolic diminuendo murmur at the base. Several fluoroscopic examinations gave evidence of enlargement of the right and left ventricles, with prominence of the aortic knob and pulmonary artery.

The patient was afebrile on admission and remained so throughout her period in the hospital, except for occasional transient rises to 100° F. Dyspnea and edema continued. The venous pressure was elevated. Vomiting was troublesome. The râles in the lungs became more marked, dyspnea and edema became more pronounced, and the patient died on Oct. 27, 1941.

At necropsy, edema was present over the feet, legs, hands, and sacrum. The right pupil was slightly larger than the left. The edge of the liver was palpable 9 cm. below the right costal margin. There were about 600 c.c. of clear yellow fluid in the peritoneal cavity, 200 to 300 c.c. in each pleural cavity, and about 100 c.c. of slightly cloudy fluid in the pericardial cavity. The heart was markedly enlarged and weighed approximately 550 Gm. The right auricle was dilated, and the right ventricle showed marked hypertrophy; its wall measured 9 mm. in thickness. The pulmonary artery and its right branch were markedly dilated. The left pulmonary artery appeared relatively small. On opening the heart and great vessels, it was noted that when a probe was passed through the pulmonary artery it extended into the aorta. The first part of the aorta was not enlarged. Just beyond the origin of the left subclavian artery, however, there was a large, sacular dilatation of the aorta (Fig. 1A). This sac extended downward and slightly to the left. On looking into the sac, the probe passed from the left pulmonary artery was seen to be protruding into the sac through an elliptical opening which measured 6 mm. in length. The edges of this opening appeared rather smooth (Fig. 1B). The sac measured 5 cm. in diameter. Its wall was inelastic. Its inner surface was wrinkled and firm, with some roughening. The external surface was firmly bound down by fibrous tissue to the surface of the left pulmonary artery. In the first part of the aorta, some pink elevated plaques were seen. There was longitudinal wrinkling of the intima which suggested syphilis. No valvular lesions were seen. There were no definite widening of the commissures of the aortic valve cusps and no narrowing of the coronary ostia. The left ventricular wall measured 1.5 cm. in thickness.

The right lung was larger and much firmer than the left. The external surface of the right lung was brown and mottled. Its cut surface was brown and firm. The left lung was more crepitant, and gray in color. The spleen weighed 125 Gm. and presented several small, wedge-shaped areas of infarction. The liver weighed 1,025 Gm. and showed gross evidence of congestion and fatty degeneration.



Fig. 1A.—Case 1. Ascending portion of aorta shown opened at "A." Aneurysm lies in transverse portion of arch of aorta and communicates with left branch of pulmonary artery. Pulmonary artery is shown opened at "P.A."

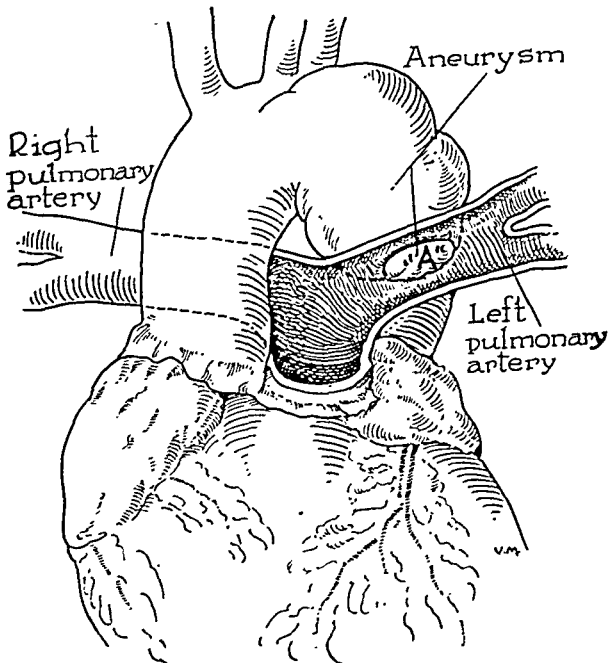


Fig. 1B.—Case 1. Diagrammatic representation, showing location of aneurysm, compression of left branch of pulmonary artery, and rupture into this vessel at "A."

Microscopically, there was marked thickening of the alveolar walls of the right lung, and an increased amount of fibrous tissue and congestion of capillaries were noted. Many of the alveoli contained "heart failure" cells. There was thickening of the vessel walls throughout.

Sections of the heart showed some endocardial thickening, and fragmentation and hypertrophy of myocardial fibrils.

In the aortic wall, well-defined focal accumulations of lymphocytes were noted in the outer media and adventitia. The lymphocytes were most numerous in the region surrounding the small vasa vasorum. There was intimal proliferation, with narrowing and stenosis of the lumina of these small vessels (Fig. 2).

Pathologic Diagnoses.—(1) Hypertrophy and dilatation of the heart, (2) saccular aneurysm of the distal part of the transverse portion of the arch of the aorta, with erosion into the left pulmonary artery, (3) chronic congestion of lungs, liver, spleen, and kidneys, (4) infarction of spleen, and (5) syphilitic aortitis.

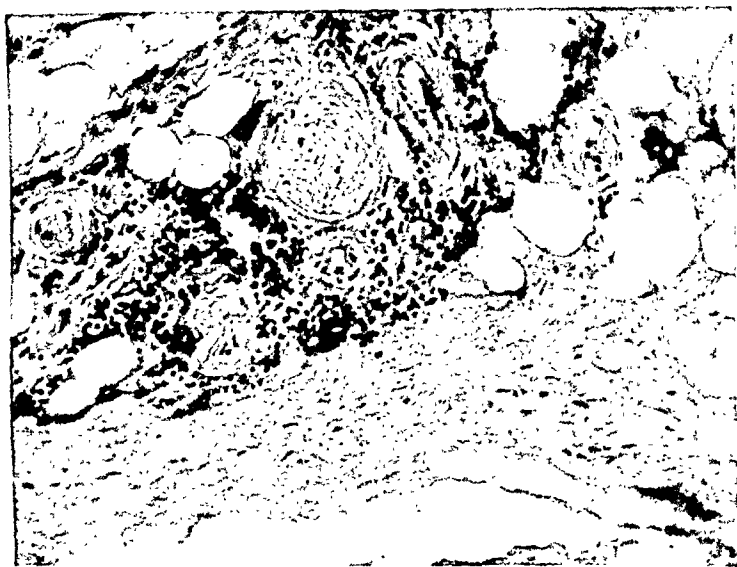


Fig. 2.—Section of wall of aorta, showing endarteritis and perivascular round cell accumulations about the vasa vasorum.

CASE 2.—The patient was a 40-year-old colored man who was admitted to Charity Hospital Jan. 2, 1942, with the history of having been perfectly well until three months previously, when he developed a slight, nonproductive cough. Five days prior to admission he noticed a "snap in his chest" which was associated with pain in the left shoulder and marked dyspnea. The dyspnea became increasingly severe. Cough persisted until the day before admission to the hospital, when the sputum was frothy and bloodtinged.

He had lost 18 pounds in the preceding month. He gave a history of having had a "chancre" ten years before, after which he received several "injections into the hip" over a period of one month.

On admission, the blood pressure was 120/70, the temperature, 99° F., and the pulse rate, 100. He was markedly dyspneic and showed slight cyanosis of the mucous membranes. The trachea was in the midline. Fine rales were scattered diffusely over both lungs. The heart was not enlarged to percussion. A loud "buzzing" sound, extending through systole and diastole, was heard over the pulmonic area. The aortic sounds were absent. A thrill, extending through systole and diastole, was felt in the pulmonic area. The liver was palpable at the costal margin.



Fig. 3A.—Case 2. Dotted lines at A represent opening into saccular aneurysm, viewed from aortic side. Aneurysm and clot contained therein are shown at B. C represents border where wall of aorta and pulmonary artery have been eroded and destroyed, with rupture into the latter vessel at its bifurcation. D shows markedly dilated opening of right pulmonary artery.

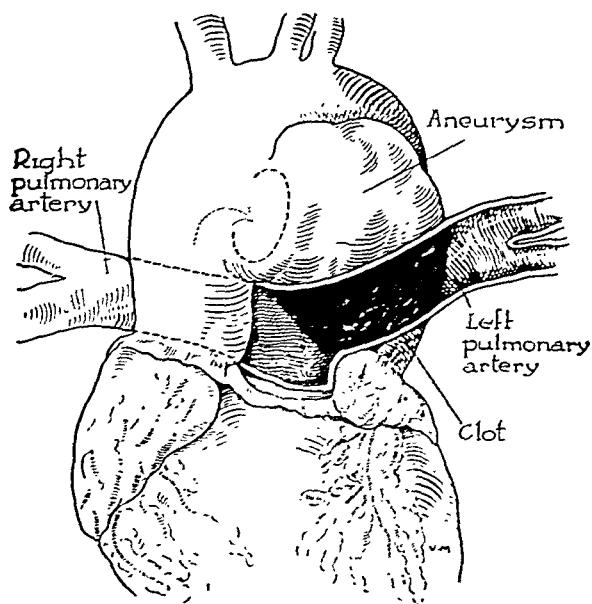


Fig. 3B.—Case 2. Diagrammatic representation, showing location of aneurysm in ascending portion of aortic arch, with compression and destruction of wall of left pulmonary artery. Rupture occurred into pulmonary artery at its bifurcation at border of the laminated clot in the aneurysm.

Laboratory examination showed slowing of the circulation time and increased venous pressure. An electrocardiogram revealed no evidence of myocardial disease. A roentgenogram of the chest showed widening of the mediastinal shadow at the base of the heart and just above this area.

The patient failed to respond to all therapeutic measures. He died Jan. 3, 1942, about fifteen hours after coming to the hospital.

Clinical Diagnosis.—Aneurysm of the aorta, with rupture into the pulmonary artery.

At necropsy, a small amount of free fluid was found in the peritoneal and pleural cavities. The heart was not particularly enlarged. There was a slight degree of hypertrophy of the walls of the ventricles. The chambers of the heart, especially the right auricle and ventricle, showed considerable dilatation. The endocardial surface was smooth and glistening. The valve cusps were not thickened. The ostia of the coronary arteries were normally patent.

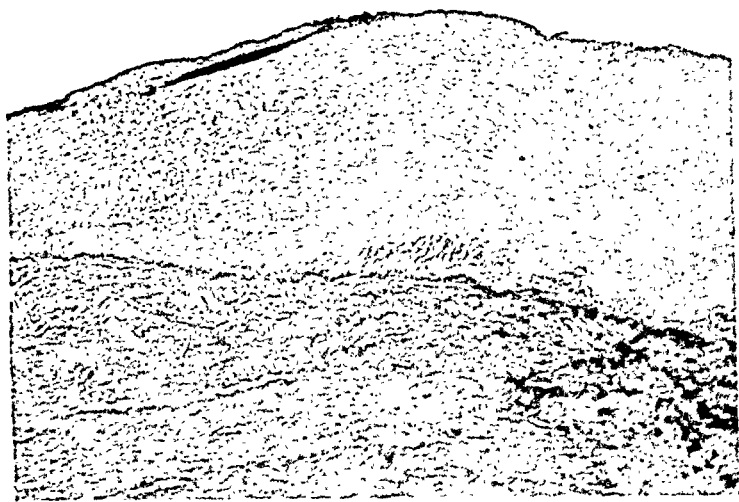


Fig. 4.—Section of wall of aorta. Upper half, showing marked thickening and proliferation of intimal structures.

On external examination of the thoracic aorta, a rather marked saccular dilatation of the ascending portion, about 3 cm. above the aortic valve, was found. This sac was pressing against the pulmonary artery. On opening both of these vessels, freshly clotted blood was seen to extend continuously from the aorta into the pulmonary artery through an opening at the margin of a lamellated clot. This lamellated clot measured 5 cm. in diameter and practically filled the depths of the saccular dilatation of the aorta, except for the area of communication into the pulmonary artery. On further examination, it was seen that the walls of both the aorta and the pulmonary artery had been completely destroyed at the site of the sac, and that the lamellated clot formed the only barrier between the two vessels over an area which measured 5 cm. in diameter (Fig. 3A). Thus, although the actual communication between the two vessels appeared to be relatively small (1 to 2 cm.), their walls were destroyed over a considerable area, making a potential communication 5 cm. in diameter. The right branch of the pulmonary artery was readily seen below and behind the site of the aneurysm. The left branch of the pulmonary artery appeared to be completely occluded at its origin by pressure of the sac (Fig. 3B). Its orifice was therefore located with difficulty. The lungs showed evidence of chronic passive congestion; this was possibly slightly more pronounced in the right lung than the left.

The intimal surface of the aorta showed the typical "tree-bark" wrinkling and thickening of syphilitic *mesaortitis*. There were also elevated pink areas and gray glistening plaques. The pulmonary artery and its right branch were markedly dilated.

Microscopically, the aortic wall showed perivascular lymphocytic infiltration and intimal proliferation of the *vasa vasorum*. There were also markedly hyperplastic areas of the intima of the aorta itself (Fig. 4). The Weigert stain showed disruption and destruction of the normal elastic fibrils, with replacement by fibrous tissue (Fig. 5).

Pathologic Diagnoses.—(1) Aneurysm of the ascending aorta, with rupture into the pulmonary artery, and (2) syphilitic aortitis.

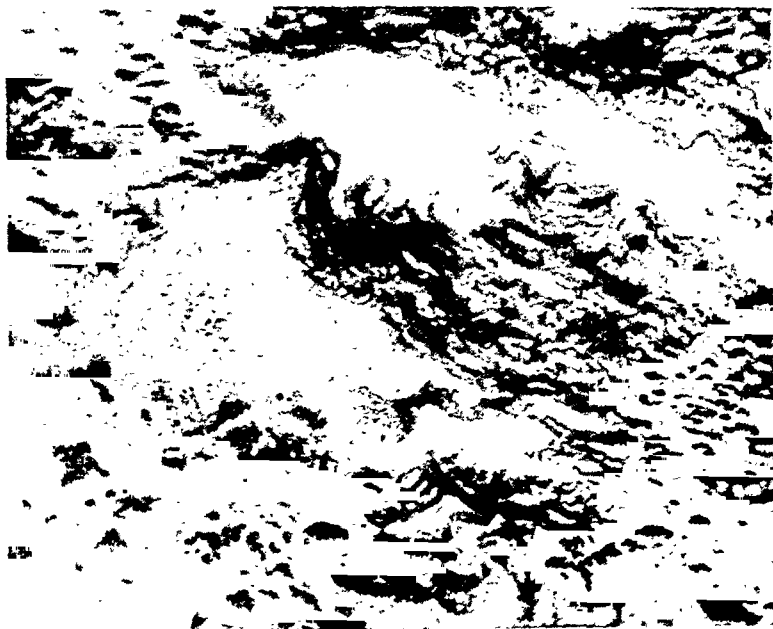


Fig. 5.—Weigert stain of section of aorta, showing disruption and destruction of normal histologic structures, especially elastic fibrils, with fibrous tissue replacement.

DISCUSSION

In a study of 1,197 cases of ruptured aneurysm of the thoracic aorta, Boyd⁶ found that in 3.7 per cent the rupture occurred into the pulmonary artery. This is in accord with Lemann's⁷ series of 529 ruptures of thoracic aortic aneurysms, in 18, or 3.0 per cent, of which the rupture occurred into the pulmonary artery. In only one of Potter's⁸ 46 cases and one of Kampmeier's⁹ 98 cases of ruptured thoracic aneurysms did rupture occur into the pulmonary artery. Woolley¹⁰ reported a series of 6 ruptured aneurysms of the arch of the aorta, of which one involved the pulmonary artery.

Kampmeier's⁹ study included a group of 1,038 cases in which the diagnosis of aneurysm of the thoracic aorta was made at the Charity Hospital in New Orleans between 1905 and 1935. In none of these did rupture take place into the pulmonary artery.

Since Jan. 1, 1935, through April 15, 1942, the following statistics have been compiled from the records of patients at the Charity Hospital:

Aneurysm of thoracic aorta (autopsy diagnosis)	121
Aneurysm of thoracic aorta (clinical diagnosis; no autopsy done)	336
Total	457
Rupture of aneurysm of thoracic aorta (autopsy diagnosis)	18
Rupture of aneurysm of thoracic aorta (clinical diagnosis; no autopsy done)	12
Total	30
Sites of rupture (autopsy diagnosis):	
Pulmonary artery	2
Great veins	3
Trachea	6
Esophagus	6
Total hospital admissions (ward patients) from Jan. 1, 1935, through April 15, 1942	447,236

Therefore, the two cases herein reported are the only ones out of a series of 1,595 cases of aneurysm of the thoracic aorta at the Charity Hospital over a period of thirty-six years in which rupture of the aneurysm into the pulmonary artery occurred. There were approximately 132 ruptures during this period, so that the incidence of rupture into the pulmonary artery was only about 1.5 per cent. This is considerably below the figures (3 per cent and 3.7 per cent) presented above.

The cases of Garvin and Siegel,¹¹ Scott,¹² Stevenson,¹³ Delp and Maxwell,¹⁴ and White, Chamberlain, and Kelson¹ illustrated this complication in its usual form, namely, rupture into the main trunk of the pulmonary artery. In the case of Korb and Ayman,¹⁵ however, the rupture occurred into the left pulmonary artery. This was the only instance of its kind in the literature, so that our Case 1 is the second to be reported.

This calls attention to the marked difference in the gross and microscopic changes in the right and left lungs and their respective pulmonary arteries in Case 1, and to a considerable degree in Case 2.

The right lung was much larger and firmer to palpation, and, microscopically, showed the "brown induration" of long-standing congestion. The left lung was smaller, and did not show such decided microscopic changes. The right pulmonary artery was markedly dilated and its wall thickened, as compared with the left pulmonary artery. All of these abnormalities, we believe, are attributable to long-standing pressure of the aneurysmal sac on the left pulmonary artery, with resulting stenosis of this vessel. Such an occurrence would bring about shunting of most of the blood from the right ventricle into the right pulmonary artery and right lung, and so place an overload upon these structures. When the rupture did occur into the left pulmonary artery, however, this mechanism would probably be altered.

It is believed that the rupture in Case 1 occurred some time before death, possibly during one of the patient's attacks of dyspnea and chest

pain some months previously. The pathologic changes were compatible with a rupture of some weeks' or months' duration.

The size of the heart, with cor pulmonale, has been discussed by Garvin and Siegel.¹¹ Cor pulmonale was well shown in Case 1, and was less marked in Case 2.

The obvious explanation is obstruction of the pulmonary artery by pressure of the aneurysm before actual communication is established. That there is, of necessity, such a period of long-continued pressure in most of these cases seems important from the standpoint of clinical diagnosis, for otherwise unexplained right ventricular hypertrophy, dilatation, or failure might thus be understood.

The clinical features of the condition have been very thoroughly discussed by Taylor,⁴ as well as by more recent writers.^{1, 12, 14} Suffice it to say that, in the cases herein reported, there were the usual dyspnea, pain in the chest, jerky pulse, and continuous murmur at the pulmonary valve area, with a systolic exacerbation.

The usual cause is syphilis. In Case 1 the Kline and Kolmer reactions were positive. In Case 2 there was a history of a chancre ten years previously. There was gross and microscopic evidence of syphilitic aortitis in both cases. Levaditi stains of the aortic wall and myocardium in these two cases failed to reveal spirochetes, perhaps because this examination was not carried out on fresh material. A Weigert elastic tissue stain of sections of the aortic wall in both cases showed the classical picture of disruption of the elastic fibers, with connective tissue replacement.

SUMMARY

Two cases of aneurysm of the arch of the aorta, caused by syphilis, with rupture into the pulmonary artery, are herewith reported. A brief review of the literature, with emphasis on the incidence of this condition, is presented. Attention is called to the very infrequent occurrence of this entity at the Charity Hospital of Louisiana, at New Orleans, as contrasted with the incidence given in other reports. Additional points of interest are that the rupture in Case 1 was into the left pulmonary artery, rather than into the main pulmonary trunk, and that the aneurysm of the aorta was in the transverse, rather than the ascending, portion. The gross and microscopic lesions indicated that the rupture might have been of some weeks' or months' duration. Also, our observations support the contention that there is a period of relative obstruction of the pulmonary vessel before it is eventually invaded, and that this produces changes which might aid in clinical interpretation before actual rupture occurs.

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THE CAPACIGRAPH-STRING GALVANOMETER FOR RECORDING ARTERIAL AND VENOUS PULSATIONS

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THE CAPACIGRAPH in combination with a galvanometer of low natural frequency has been used to record the surface displacements over the external jugular vein.¹ Substituting a string galvanometer for the galvanometer of low natural frequency provides a combination with a figure of merit which is limited only by the dynamic qualifications of the string galvanometer. The combination permits one to feed separately or simultaneously to the string galvanometer the potential variations derived from the capacigraph or from the heart. It is thus possible to make at will, and with relative ease, separate recordings of surface displacements and the electrocardiogram, or to record the resultant of the two simultaneously. When combination recordings are made, the R wave of the electrocardiogram is used as a positive (time-electrical) reference point in the analysis of complex surface displacements produced by in situ blood vessels during the cardiac cycle. The R wave may be used in this manner, but the other components of the electrocardiogram are usually not recognizable.

It is well known that the skin of the neck undergoes displacements caused by the pulsations in underlying vessels. The skin which overlies regions in which there are no large vessels also undergoes displacement during the cardiac cycle; this is caused partly by the pulsations of smaller vessels, and partly by pulsations from adjacent regions which contain large and small blood vessels. Each vessel pulsates in accordance with known tension changes which are transmitted to them and developed within them during each cardiac cycle. When the "pickup plate" is placed over the right external jugular vein, with the patient supine, a curve is obtained which has the general characteristics shown in Fig. 1. Three principal waves are recognized; they correspond to the A, C, and V of the venous pressure pulse obtained by other methods. When the pickup plate is placed over the right common carotid artery, a curve is obtained which shows the general characteristics of Fig. 2. Three waves are again recognized; however, the first is known to be auricular in origin, and shows a variable amplitude, depending upon the individual subject. So far, it has been impossible to obtain by means of the free plate approach, and under the conditions of observa-

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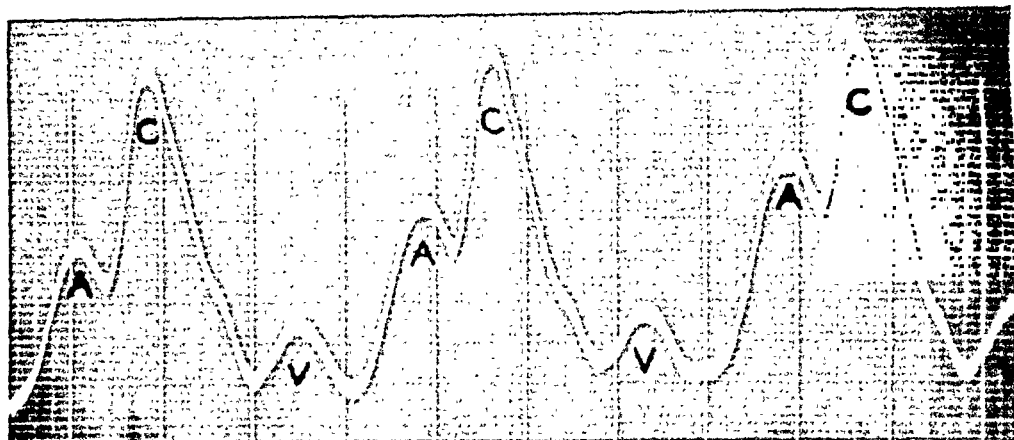


Fig. 1.

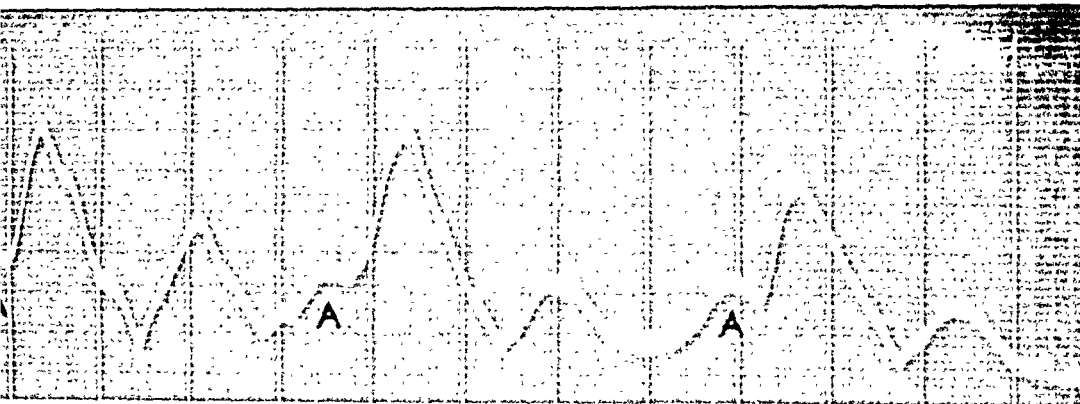


Fig. 2.

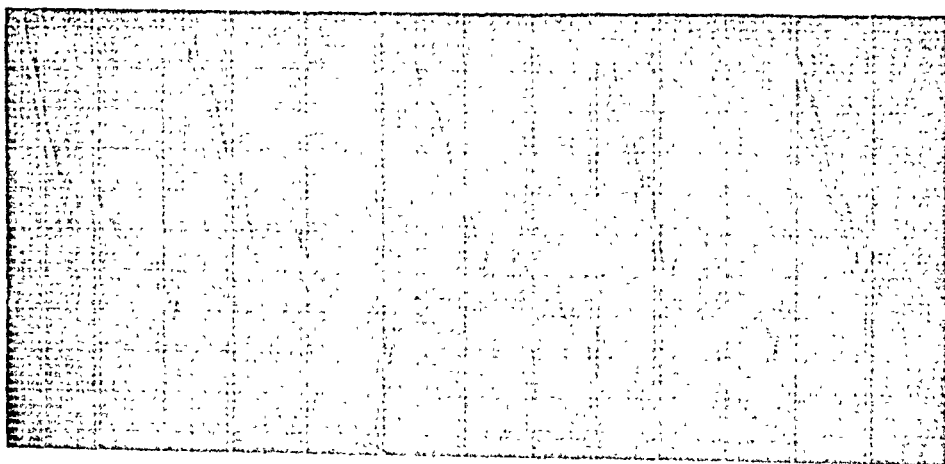
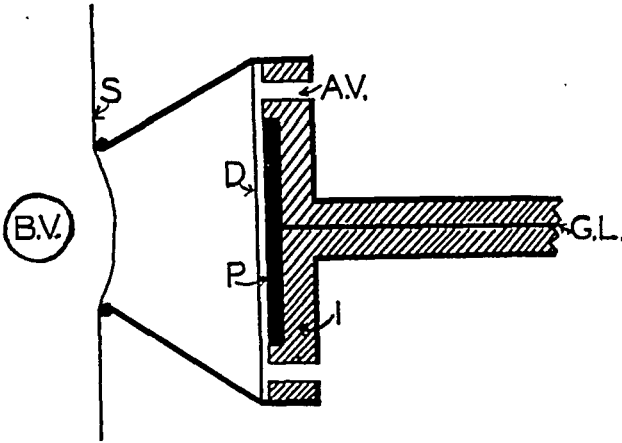


Fig. 3.

tion, an arterial neck pulsation in which there is no venous A component. On the other hand, the curve of Fig. 3 was obtained from the right common carotid region by a modified pickup plate upon which sufficient tension was applied to block the venous component. The general configuration resembles that of the arterial pressure pulse obtained by other



A.V. - AIR VENT
 D - DIAPHRAM
 P - PLATE
 I - INSULATION
 G.L. - GRID LEAD
 S - SKIN
 B.V. - BLOOD VESSEL

Fig. 4.

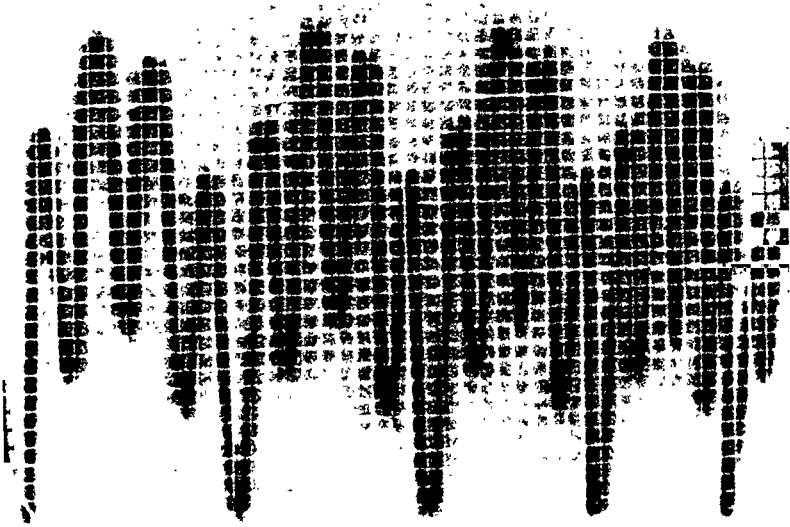


Fig. 5.

methods. The modified plate was devised on the condenser microphone principle (Fig. 4). The dynamic qualifications of this unit are good. Fig. 5 illustrates the simultaneous response to two sounds of 4000 and 16,000 V/S respectively, as registered by the cathode-ray oscillograph.

Fig. 6 shows the combined pulse and electrocardiogram which was obtained by placing the free pickup plate over the right external jugular vein. The R wave occurs during the first wave of the three-wave dis-

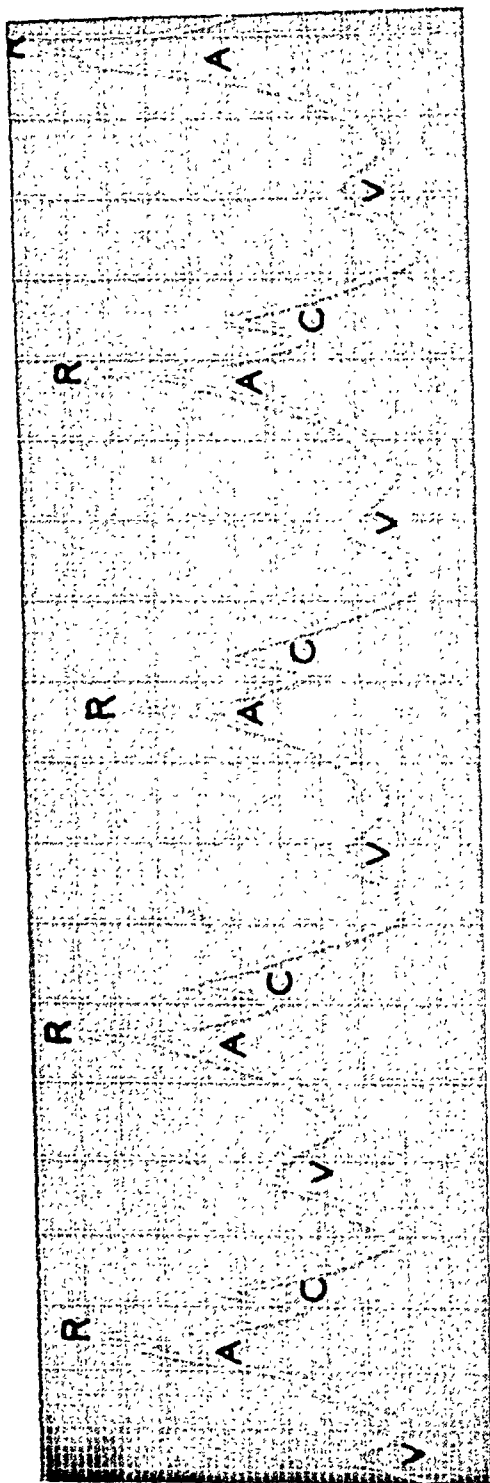
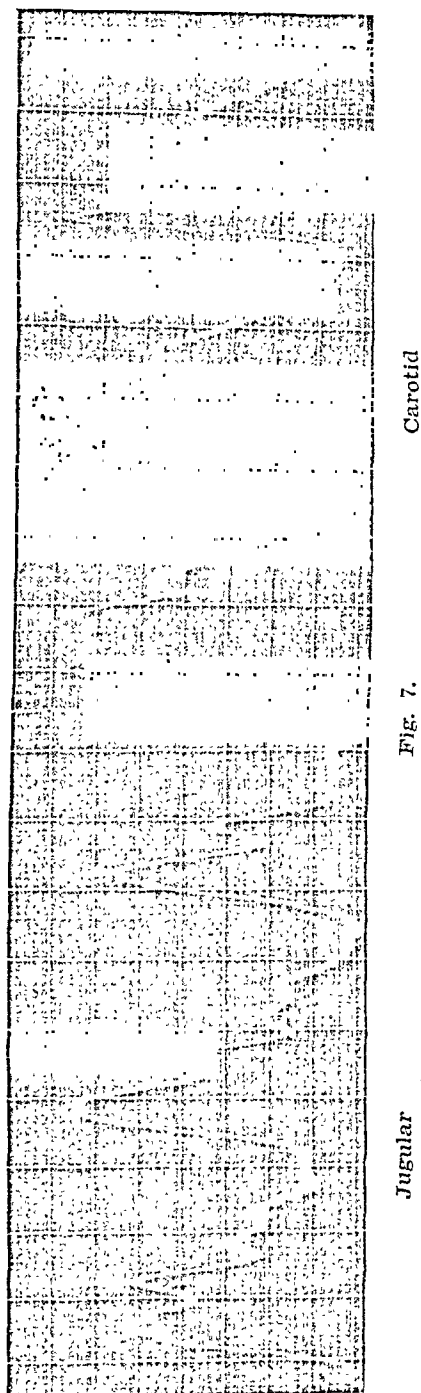


Fig. 6.

placement complex. The apparent relationship of the electrical change (ventricular in origin) and the mechanical displacement (auricular in origin) is in part due to the fact that excitation develops before the onset of the mechanical response, and in part due to the time required



for the propagation of the pulse wave to the region underlying the pickup plate. By this means, the velocity of the pulse wave may be ascertained. The plate can be shifted nearer to, or away from, the origin of the force producing the displacement. As an index, the R wave

and its temporal relationship to a well-marked displacement component may be ascertained; then, upon shifting the plate, any change in time relationship is caused by the increase or decrease in the time necessary for the pulse wave to travel between the two points.

However, for complete accuracy, an additional factor must be taken into account: the distance through which the pulse wave is propagated may remain constant, but the interval which elapses between the development of the excitation wave and its associated electrical potentials and the mechanical response may vary. Fig. 6 bears this out. The relationship of R wave to A wave varies slightly with each beat of the heart in a cyclic manner over a period of five cardiac cycles, which, in this case, is roughly equivalent to one respiratory cycle. It is assumed that the factors which cause sinus arrhythmia produce these variations.

Fig. 7 shows the pulsatile changes which were recorded from the neck of a pregnant patient with rheumatic heart disease; the heart was 37 per cent oversize, and there were aortic and mitral lesions.

No attempt is made at this time to correlate the clinical, physiologic, and recorded data. The recordings are presented to show the potential diagnostic uses of the capacigraph-string galvanometer.

SUMMARY AND CONCLUSIONS

A new and useful method for the study of normal and abnormal cardiodynamics is presented.

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Special Articles

REPORT OF THE COMMITTEE OF THE AMERICAN HEART ASSOCIATION ON THE STANDARDIZATION OF ELECTROCARDIOGRAPHIC NOMENCLATURE

INTRODUCTION

IT IS nearly half a century since Einthoven first employed the letters P, Q, R, S, and T to designate the component deflections of the curves which he obtained by computing and eliminating the distortion present in records of the normal heart beat taken with the capillary electrometer. After he had invented the string galvanometer and was able to record the human electrocardiogram in undistorted form he continued to use these symbols, and eventually added to their number by assigning the letter U to the low-voltage deflection often present in early diastole, and by accepting the designation T_a , previously employed by Hering, for the inconspicuous final component of the auricular complex.

This system of nomenclature has been in practically universal use since the very beginning, and it is permanently imbedded in a vast and important literature, which all serious students of electrocardiography must frequently consult. In spite of the tremendous growth of this science in the recent past, it has continued to serve its purpose more than reasonably well. Some have found it unsatisfactory in certain respects, and have tried to replace it with an entirely different terminology, but such efforts have met with no success and are now of interest chiefly from the historical standpoint. Under these circumstances it seems essential that, in attempting to standardize electrocardiographic nomenclature, we respect usages that are long standing and generally accepted, and make only such recommendations as may be required to meet urgent needs of the present and immediate future. It is desired that all concerned clearly understand the causes of dissatisfaction which have led to a demand for some action of this sort.

Much of this dissatisfaction is clearly dependent upon the circumstance that electrocardiographic nomenclature, like any other language, is continuously changing. It must grow and expand with the science which it serves, and can be stabilized only temporarily. With the advance of knowledge the terms and symbols introduced by our predecessors have been utilized to meet new needs and have acquired meanings which they did not originally possess and which are not exactly the same for all workers. We propose to redefine those terms that are in general use so that misunderstanding may be avoided. The introduction or recommendation of new terms which have not been widely

adopted in response to an imperative need would be more confusing than helpful.

It was primarily to facilitate the description and discussion of the form of the electrocardiogram that Einthoven first assigned letters to its individual components. It is important that this function of our nomenclature should be kept in mind. The deflections to which he gave names differed one from another in various ways; in size, in direction, in shape, in duration, in sequential position, and in their relations to other events in the cardiac cycle. All the components originally named were no doubt regarded as fundamentally different in origin. It should be emphasized that neither the observed differences nor the differences in origin inferred can be considered all of the same sort or all equally significant.

It is clearly desirable that deflections alike in origin always be given the same name, and that deflections unlike in origin bear different names. Both Einthoven and Lewis after him recognized the validity and importance of this principle. The former went considerably farther than the latter in his efforts to avoid violating it, and his writings suggest that it was chiefly for this reason that he never solved to his own complete satisfaction the problem of adapting his nomenclature to electrocardiograms of unusual or abnormal outline. The difficulty seems to have been that he did not fully realize that the symbols he was using differed greatly in value; that the phenomena which they represented were by no means equal in rank.

When dealing with initial ventricular deflections conspicuously different from those to which the letters Q, R, and S were first assigned, he usually did not attempt to name them individually but made use of the symbol (QRS) to designate this group of deflections as a whole. This solution of the problem surrendered the advantages which he had gained originally by naming the components of the QRS complex.

In the case of bundle branch block of the common type, he went farther still, and often labeled the first large deflection of the essentially diphasic ventricular complex *A* and the large final deflection *B*. For a similar reason Lewis assigned the symbols Q', R', S', and T' to the components of electrocardiograms of this kind. Few authors have followed Einthoven and Lewis in giving distinctive names to the ventricular deflections of branch block curves. According to our present conceptions the final ventricular deflection always represents the same physiochemical process. By always calling it the T wave, we emphasize this important truth. By giving it one name when normal and a variety of others when abnormal we should obscure a likeness which is fundamental for the sake of making distinctions which are, by comparison, trivial. These remarks apply with equal force to the problem presented by normal and abnormal QRS complexes.

In cases of pronounced axis deviation, Einthoven used the letter R to designate the chief QRS deflection regardless of whether it was upward

or downward. Lewis, on the other hand, called this deflection R when it was upward and S when it was downward, and the vast majority of recent writers have done likewise. From time to time, however, attempts have been made to revive Einthoven's point of view.

In the last few years differences of opinion have arisen as to what constitutes a Q deflection and what an S deflection. When the QRS complex consists of a single downward deflection, some writers call this deflection S on the ground that a downward deflection should not be labeled Q unless it is followed by an upward deflection. Others call it Q on the ground that this name should be given to every downward deflection not preceded by an upward deflection.

By far the greater part of the dissatisfaction with our electrocardiographic nomenclature has clearly been due to a lack of agreement as to what principles should govern the assignment of the letters Q, R, and S to the components of the QRS complex. The symbols P, T_a, QRS, T, and U have long been used in the same way by everyone and present no difficulties. The electrocardiographic components which they represent may be regarded as at least approximately equal in rank. Each has a characteristic contour and a distinctive relation to other events of the cardiac cycle. According to our present conceptions each has a distinctive origin. The first (P) is held to represent all those electrical forces produced by depolarization (activation) of the auricular muscle; the second (T_a), all those electrical forces produced by repolarization of the auricular muscle. The third (QRS) and fourth (T) are held to represent all the electrical forces generated when these same physiochemical changes take place in the ventricular myocardium. The last (U) is less well understood; it apparently depends upon some sort of readjustment of the polarization of the ventricular muscle. Since these physiochemical changes are closely related to the mechanical activities of the heart, and necessarily occur whenever the heart beats, their electrical representatives can never be actually absent in any lead. Some may, however, be isoelectric or of such low voltage that they are imperceptible, and it often happens that a small deflection is difficult or impossible to detect because it is superimposed upon a much larger one. Whatever the standpoint adopted, each of these components of the electrocardiogram is clearly entitled to a distinctive name. It is obvious that there is little danger of mistaking one of them for any of the others.

The individual components of the QRS complex are not entities of the same sort. They vary in number from subject to subject and from lead to lead. They have not been related to different events of the cardiac cycle, nor have they been shown to depend upon the activities of distinct subdivisions of the ventricular muscle. None of them has a distinctive contour. They differ one from another chiefly in direction and in sequential position, and can not be easily defined except in terms of these differences. All these deflections are alike in origin

in the sense that all are produced by electric forces generated by the spread of the excitatory process over the ventricular muscle. They can differ in origin only as regards the particular fraction of these forces which each represents. The individual fibers which contribute the elementary forces responsible for a given component in a given lead do not all lie in the same part of the ventricular myocardium. None of the QRS components in any lead has a simple anatomical basis of this kind which would make its origin distinctive in the anatomical sense. The origin ascribed to any component is mainly, for this reason, dependent to a large extent upon the point of view adopted, and no one particular point of view has gained such wide acceptance as to make it pre-eminent.

It has been suggested that the QRS interval should be subdivided in one way or another, and that names should be assigned to parts of the QRS complex solely on the basis of the particular subdivision of this interval within which they fall, rather than to the separate deflections of which it is composed. This suggestion is derived from the view that any part of the QRS complex written during a given interval of time in one lead is identical in origin with those parts of the QRS complex written during the same interval in other leads in the sense that it is produced by the same electrical forces. It is assumed that all the elementary electric forces present at a given instant are equally effective, in proportion to their magnitude, in all the leads under consideration, or that, so far as these leads are concerned, they are equivalent to a unique resultant electromotive force which may be substituted for them. Einthoven's equilateral triangle defines a resultant electromotive force, the cardiac vector, which may be substituted for the actual electromotive forces when dealing with limb leads, if the assumptions upon which this triangle is based may be regarded as representing the true situation with sufficient accuracy for the purposes in mind. Now that it is customary to take precordial leads to which it is not applicable, as well as limb leads, it is not desirable to enthrone this point of view in our nomenclature and disregard others which are equally legitimate.

For this reason, and because it greatly complicates the assignment of the letters Q, R, and S to the initial group of ventricular deflections and the description of the form of the QRS complex, we believe that a downward deflection should never be labeled R on the ground that it occupies the same interval and represents the same resultant forces as an upward deflection in another lead to which this letter has been appropriately assigned. It is equally disadvantageous to label an upward deflection Q or S because it corresponds in time to a downward deflection in another lead to which the same letter has previously been allotted.

The considerations mentioned and the multiplicity of leads now in use fully justify the labeling of the QRS components of one lead without reference to the number or character of the QRS components in any

other lead. The allocation of the symbols employed should be determined solely by the direction and sequence of these deflections in the lead under consideration.

RECOMMENDATIONS

1. The symbols P, T_a, QRS, T, and U should be used to represent those deflections or groups of deflections to which they were originally assigned, both when the electrocardiogram is normal and when it is abnormal.

2. In the majority of cases the QRS complex is superimposed upon the T_a deflection. For this reason the level of reference from which the voltage of the QRS deflections is measured should be the level at which the first of these deflections begins. The voltage of an upward QRS deflection should be measured by estimating the vertical distance between the upper edge of the trace at the beginning of the QRS interval and the upper edge of the trace at the point where the deflection reaches its maximal elevation. The voltage of a downward deflection should be determined by estimating the vertical distance between the lower edge of the trace at the beginning of the QRS interval and the lower edge of the trace at that point of the deflection which is farthest from the reference level.

3. In order to indicate how the QRS complex should be subdivided for the purpose of assigning symbols to the deflections which it displays, we may describe a QRS complex which has three components in the following terms: The first deflection begins at the onset of the QRS interval when the trace first leaves the reference level. From this point the trace rises or falls to a turning point, where the direction of its motion is reversed. It may pass through a second or third turning point before crossing to the opposite side of the reference level.* At this crossing the first deflection ends and the second begins. The second deflection, necessarily opposite in direction to the first, must display one turning point and may display many; it does not end until the trace crosses the reference level for the second time. The third deflection begins at the second crossing and ends at the RS-T junction. No part of the QRS complex which does not display at least one turning point should be considered a separate deflection. If the RS-T junction is displaced and this junction and the last turning point lie on opposite sides of the reference level, that portion of the trace which lies between the last crossing and the RS-T junction should be considered part of the deflection to which the last turning point belongs.

The earliest QRS deflection which lies above the reference level should be labeled R. Any downward deflection which precedes R, so defined, should be labeled Q. The first of any downward deflections which may

*When the trace is descending it crosses the reference level at the instant when its lower margin reaches a position below that which it occupied at the beginning of the QRS interval. When the trace is ascending it crosses the reference level at the instant when its upper margin reaches a position above that which it occupied at the beginning of the QRS interval.

follow R should be labeled S. The first of any upward deflections which may follow S should be labeled R', and the first of any downward deflections which may follow R' should be labeled S'. If it is necessary to label still later deflections of the QRS group, the symbols R," S," etc., should be used in accordance with the same principles. When R is absent, so that the QRS complex consists of a single downward deflection, this deflection should be labeled QS. In statistical studies QS, Q, and S deflections should be considered separately.

A deflection is "notched" when it displays more than one turning point on the same side of the reference level. A deflection is "slurred" when it displays a distinct and local "thickening" on either limb or at its apex, due to a sudden and pronounced change in the slope of the curve, or, in other words, in the rate at which the trace is rising or falling.

When the form of the QRS complex varies from moment to moment because of the effect of the respiratory movements upon the position of the heart, or for some similar reason, the classification of this complex should be determined by the variety of complex which is most abundant, or, if no type is numerically predominant, by the outline of the complexes which are of intermediate form. Very small QRS complexes (largest deflection less than 5 mm.) which display more than three components or multiple slurring and notching should be classed as "small and bizarre" or "vibratory."

4. The term RS-T junction should be used to indicate the point or shoulder which marks the end of the QRS complex, i.e., the point where the steep slopes of the QRS deflections are more or less abruptly replaced by the more gradual slopes which precede or comprise the first limb of the T wave. In many electrocardiograms the RS-T junction is followed by a nearly horizontal or gently sloping segment which lies on, above, or below the reference level, and ends with the onset of a much steeper slope that rises or falls to the apex of T. It is agreed that the term RS-T segment is a useful name for this part of the ventricular complex when it exists, even though it is proper to regard it as the earliest part of the T deflection. When there is no point between the RS-T junction and the apex of T at which a sharp change in the slope of the trace occurs, this part of the ventricular complex should be called the first limb of the T wave. When the term RS-T segment is used without reference to some particular electrocardiogram or to some particular class of electrocardiograms, it should be understood to refer merely to that part of the ventricular complex which immediately follows the RS-T junction. The reference level for the measurement of the displacement of the RS-T junction should be the same as the level of reference for the measurement of the QRS deflections. The level of reference for the measurement of the RS-T segment, the T wave, and the U wave should be the isoelectric level when this can be determined; otherwise it should be the level of the

trace at the beginning of the QRS interval. The isoelectric level is the level of the trace at the beginning of the P wave when the P wave occurs in its normal relation to the QRS deflections and is not superimposed on T or U.

5. The term "diphasic T waves" should be applied to those final ventricular deflections which present two distinct turning points, one on each side of the level of reference. If the earlier turning point lies below this level, and the latter above it, the diphasic T wave may be said to be of the minus-plus ($- +$) type. If the reverse is the case, it may be said to be of the plus-minus ($+ -$) type. When the term diphasic is used with reference to other deflections, to the QRS complex, or to the ventricular complex as a whole, it should be used in the same sense.

6. When applied to the QRS complex, the T deflection, to any other electrocardiographic component, or to RS-T displacement, the term "concordant" should signify that the largest deflection or displacement is in the same direction in Lead III as in Lead I. Under the same circumstances the term "discordant" should signify that the largest deflection or displacement in Lead III is opposite in direction to that in Lead I.

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SECOND SUPPLEMENTARY REPORT BY THE COMMITTEE OF THE AMERICAN HEART ASSOCIATION FOR THE STANDARDIZATION OF PRECORDIAL LEADS

EARLY in 1938 the Committee of the American Heart Association for the Standardization of Precordial Leads and a similar committee representing the Cardiac Society of Great Britain and Ireland made joint recommendations with reference to a single precordial lead for routine use. In a supplementary report published in the same year,* the American committee recommended that when multiple precordial leads were taken the precordial electrode be paired either with an electrode on the left leg or with a central terminal connected through equal resistances of 5,000 or more ohms to three electrodes, one on the right arm, one on the left arm, and one on the left leg. Six precordial points were recommended as suitable locations for the precordial electrode,† and these may be referred to as the C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 positions. In the last few years, the number of electrocardiographers who have abandoned single in favor of multiple precordial leads has rapidly increased, but there has been no uniformity as regards the number of leads taken, the location of the remote electrode paired with the precordial electrode, or the locations of the precordial points regularly explored.

There has been a persistent demand that some further action be taken with reference to the standardization of precordial leads. The undersigned have, therefore, consulted, and have attempted to reach an agreement with reference to the more important questions that have arisen in connection with this problem. It is agreed that many of these questions must be left unanswered until our knowledge of the precordial electrocardiogram is far more complete than at present. A great deal of methodical painstaking work is urgently needed with reference to the best location for the remote electrode, the desirability of taking precordial leads routinely, and the best combination of locations for the precordial electrode. The present situation is not, however, due solely to inadequate information but also to a lack of complete agreement as to exactly what is meant by "best combination" and

*AM. HEART J. 15: 235, 1938.

†It has been pointed out to us that the meaning of the last sentence of the third paragraph of our previous supplementary report is not clear. The correct interpretation of this sentence is as follows:

When the letters and subscripts specified are employed, it shall be understood that in the case of the sternal leads the precordial electrode has been placed in the 4th intercostal space, and that in the case of the other leads it has been placed upon a line drawn from the left sternal margin in the 4th intercostal space to the outer border of the apex beat and continued around the left side of the chest at the level of the apex beat. When the apex beat cannot be satisfactorily located, this line should be drawn from the left sternal margin in the 4th intercostal space to the point where the left midclavicular line crosses the center of the 5th intercostal space, and should be continued around the left side of the chest at the level of this point.

similar terms when used with reference to precordial leads, and as to whether the questions at issue are to be decided on empirical grounds alone or, if not, as to what basic principles should be given important consideration. The recommendations which follow must, for these reasons, be considered merely tentative.

The Committee is agreed that a single precordial lead from the region of the cardiac apex, or from any other part of the precordium, is inadequate. When multiple precordial leads are taken, it is found that in the vast majority of cases the extreme right side of the precordium and the extreme left side of the precordium yield QRS complexes of more or less opposite form. Leads from a usually small region lying between those from which complexes of opposite types are obtained customarily yield complexes of intermediate or transitional form, which are often difficult to interpret when curves from points farther to the right and from points farther to the left are not available for comparison. The location and size of the region from which transitional complexes are obtained vary greatly from case to case, and are not entirely constant in one and the same subject. When single precordial leads are taken from the outer border of the apex beat, the exploring electrode is, in actual practice, sometimes placed to the right of the region of transition mentioned and sometimes to the left of it, or within it. In serial observations on the same subject inaccuracy in placing this electrode or an alteration in the size or location of the region in question may be responsible for striking changes in the form of the curve obtained by what is technically the same lead.

This is only one of the causes for dissatisfaction with routine apical leads. When all cases are considered, regardless of whether the standard leads are normal or abnormal, it is perhaps true that a lead from the region of the apex or from the left anterior axillary line at the level of the apex will display abnormalities of the ventricular complex more often than any other single precordial lead. When, however, only those cases in which the limb leads are normal are considered, this is certainly not the case. It is now clear that when the standard limb leads are normal, the precordial leads most likely to yield significantly abnormal curves are those from points lying between the left sternal border and the midclavicular line. Consequently, single apical leads most often fail completely in those cases in which multiple precordial leads have most to offer.

The Committee believes that three is the least number of precordial leads that can be regarded as satisfactory for general purposes. It suggests that those who wish to reduce the number of such leads to a minimum take leads from the C_1 , C_3 , and C_5 positions. All are urged to take additional leads whenever possible. A lead from the C_2 or a lead from the C_4 position may show diagnostic abnormalities when equally significant changes fail to occur in other leads. Those who follow our recommendations must remember that inversion of the T

deflections in leads from the C_1 position is frequently encountered in normal adult subjects. It is believed that those who have had little experience with multiple precordial leads would gain much worthwhile information by taking a full set of six precordial leads on a few normal subjects and on a series of patients with known cardiac abnormalities of the commoner types.

It is agreed that the information available does not permit a definite decision on empirical grounds as to the best location for the remote electrode with which the exploring or precordial electrode is paired. It is recommended that the precordial electrode be paired with an electrode on the right arm, with an electrode on the left leg, or with a central terminal connected through equal resistances of 5,000 or more ohms* to three electrodes: one on the right arm, one on the left arm, and one on the left leg. Some, but not all, members of the Committee who formerly placed the remote electrode on the left leg now prefer to place it on the right arm. It has been observed that when the precordial electrocardiogram is judged by the normal standards at present available, a lead from a given point on the precordium may yield an abnormal curve if the exploring electrode is paired with a left leg electrode (CF lead) even though the curve obtained from the same point by using the right arm electrode as the reference point (CR lead) is within normal limits. The opposite situation may also arise. It has also been observed that in certain cases of cardiac infarction in which diagnostic changes are present in the standard limb leads, CF leads display the most striking, and CL leads (leads from the precordium to a left arm electrode) the least striking, changes. These observations can not, however, be interpreted as indicating that CF leads are always more reliable in the diagnosis of infarction than precordial leads of other kinds. There will be less confusion with reference to the effect of the remote electrode if it is clearly understood that each CR lead is equal to the corresponding CF lead plus standard Lead II; that each CL lead is equal to the corresponding CF lead plus Lead III; and that each central terminal lead is equal to the corresponding CF lead plus one-third the sum of Leads II and III, and is the algebraic mean of the CR, CL, and CF leads from the same precordial point.

The Committee does not desire at this time to make any recommendation bearing on the question as to whether precordial leads should be taken routinely or in selected cases only. It believes that precordial leads are most likely to yield information of diagnostic importance under the following circumstances: (1) Whenever myocardial infarction is suspected or must be considered a possibility; (2) whenever myocardial disease is suspected or must be considered a possibility and

*Recent observations indicate that in the vast majority of cases, if not in all, the omission of these resistances has no appreciable effect upon the form of the precordial curves obtained. Consequently, it may be satisfactory to connect the central terminal directly to the three extremity electrodes without the use of intervening resistances of any kind. Further studies should be made before this method is generally adopted.

other methods of examination yield no unequivocal evidence of cardiac disease; (3) whenever it is important to distinguish between right and left ventricular hypertrophy or between right and left bundle branch block and this can not be satisfactorily done by other means; (4) whenever for any reason a complete cardiac study is indicated.

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Clinical Reports

A CASE OF TRICUSPID INSUFFICIENCY WITH UNUSUAL VENOUS PULSATIONS IN THE EXTREMITIES

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DISEASE of the tricuspid valve and its clinical aspects have been described and discussed fully, and the criteria for diagnosis have been clearly outlined.¹⁻⁵ Pulsation of the neck veins is one of the important features of the syndrome. However, pulsations of the veins in the extremities have been less frequently noted, and especially pulsations in the veins of the lower extremities, the occurrence of which is apparently much less common. We have recently had the opportunity of observing a patient with tricuspid insufficiency who presented remarkable pulsations in varicose veins of the legs, and the apparent rarity of this condition seems to warrant this report.

CASE REPORT

S. M., a 52-year-old Jewish housewife, was admitted to another hospital January 19, 1933, complaining of cough and fever. Two weeks before, she had had an attack of pain in the chest which was typical of coronary occlusion. She had been improving until the day before admission, when she developed a cough and a rise in temperature to 103.6° F. Physical examination revealed cardiac enlargement without murmurs, but over the middle of the sternum there was a scratchy systolic sound which was thought to be a pericardial friction rub. There was consolidation of the upper lobe of the left lung, and a small amount of fluid was present at the base of the left lung. The liver was not enlarged and there was no peripheral edema. She was discharged after a hospital stay of forty-eight days. The diagnosis was coronary thrombosis and infarction of the left lung.

The patient was readmitted to the same hospital four years later because of congestive heart failure. The heart was enlarged as before. At this time a blowing systolic murmur at the apex, a rough systolic murmur at the base, and a blowing diastolic murmur at the aortic area were described. The heartbeat was totally irregular. The liver was enlarged, smooth, and soft, but did not pulsate. There were slight edema of the extremities and large varicose veins of the legs. The edema disappeared, but hepatomegaly persisted, and, after six weeks, she was discharged and advised to remain in bed.

She was admitted to the same hospital, for the third time, four months after her second admission, again with congestive heart failure. Examination revealed marked arterial pulsations in the neck, but there was apparently no venous engorgement. At this time systolic and diastolic murmurs were heard at both the apex and the base. While in the hospital an intrinsic pulsation of the liver was noted for the first time, and, although the other gross signs of cardiac insufficiency

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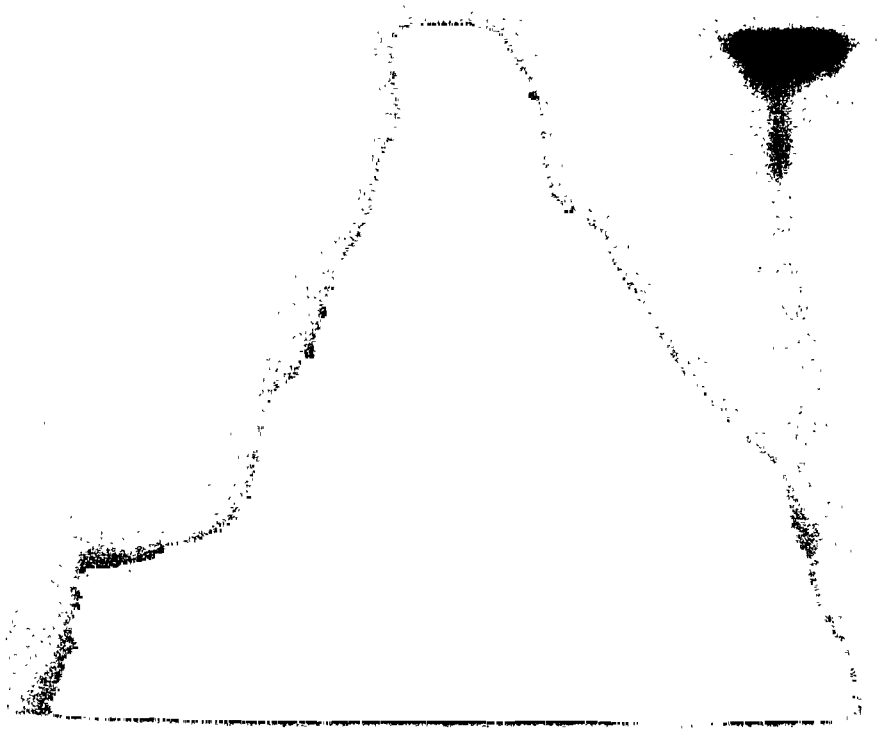
over it a loud systolic murmur could be heard. No murmur was heard in the popliteal space, and femoral arterial pulsations on both sides were vigorous.

Examination of the blood revealed a moderate hypochromic anemia. Chemical studies of the blood showed nothing abnormal. Urinalysis was negative except for a one-plus reaction for albumin. A roentgenogram of the chest showed great enlargement of the heart and calcification of the aorta. There was a large hydrothorax on the right, with congestive changes in both lungs. Fluoroscopic examination revealed that both the right and left sides of the heart were enlarged; both borders moved in very slow but forceful pulsations. The same pulsations were noted along the right side of the diaphragm, where they had a downward direction. The pulsations of the aorta were less in amplitude. There was no definite evidence of pulsation along the right border of the upper part of the mediastinum. These ob-



Fig. 1.—The roentgenkymogram shows pulsations of increased amplitude, especially in the region of the right ventricle. The ventricular pulsations are slightly irregular in amplitude. The pulsations of the aorta, superior vena cava, and the diaphragm are synchronous and large.

servations were interpreted as being indicative of disease of the tricuspid valve, with hepatic pulsation. Roentgenkymographic examination of the heart (Figs. 1 and 2) revealed that the heart was enlarged in all its diameters. The right ventricle was markedly enlarged and showed increased pulsations. These pulsations were slightly irregular in amplitude. The pulsations of the diaphragm, aorta, and superior vena cava were synchronous and large in amplitude. All this again suggested disease of the tricuspid valve. The venous pressure, measured with the skin of the back in the interscapular area as the reference point,⁹ was persistently elevated, in both the arms and legs. In the arms the venous pressure varied between 90 and 170 mm. of saline above the normal, and in the femoral veins it remained at about 200 mm. of saline above the normal level. There was a systolic pulsation in the manometer of 10 to 20 mm. of saline with the needle in either the antecubital or femoral vein. The circulation rates were increased.^{10, 11} The arm-to-tongue time varied between



without previous cardiac complaints, experienced a sudden attack of substernal oppression and collapse that was regarded as indicative of myocardial infarction. Subsequently she was thought to have had pulmonary infarction. No heart murmurs were recorded by competent observers at that time. During the ensuing eight and three-quarters years she had been limited to a semi-invalid existence because of cardiac insufficiency, and had been hospitalized twice because of heart failure, on which occasions the progression of the degree of heart failure and the development of various cardiac murmurs had been noted. Four years before admission to the Baltimore City Hospital her liver was found to be enlarged and pulsating, but it was not until her last hospital admission that the extreme pulsations in the varicose veins of her legs had become evident and the diagnosis of tricuspid insufficiency was considered.

It is difficult to conceive of rheumatic valvular disease of such extent developing in a 60-year-old person who was known to have had no cardiac murmurs at the age of 52. That this patient had arteriosclerotic heart disease, possibly one or more myocardial infarctions, and marked cardiac dilatation and hypertrophy of long standing seems probable. The development of cardiac murmurs can be explained by cardiac dilatation and valvular sclerosis, and possibly calcification. A further possibility is that there was an embolus in one of the larger branches of the pulmonary artery at the onset of her illness, with the subsequent development of pulmonary hypertension and right-sided heart strain, and that this was responsible for the clinical manifestations at the time of her admission to this hospital. It is the pulsation in the varicose veins of the legs which is of greatest interest, and with this we are primarily concerned in this report. Although pulsations in the cervical veins almost always accompany tricuspid disease, similar pulsations in the veins of the extremities are less common. Kerr and Warren¹² noted pulsations in the veins of the arms and on the dorsum of the hand in a series of patients with heart failure and relative tricuspid insufficiency, and such pulsations in the larger veins of the upper extremities have been noted by others, but visible and palpable pulsations in the veins of the lower extremities are less common. According to Kerr and Warren,¹² Friedrich, in 1866, reviewed the literature thoroughly for venous pulsations in the extremities, and he cited Marey, who, with Gaubler and Verneuil, noted pulsations in varicose veins of the leg in one case. Teufl,¹³ in 1936, in a study of 32 cases of pulsating veins of the extremities, found 16 cases of pulsating varicose veins. This would seem to indicate that such pulsations in the lower extremities are not at all rare, but rather are either overlooked or neglected. Hallock and Clarke¹⁴ have recently reported a case of pulsation in the veins of the neck, retinae, and upper extremities, and in varicose veins of the lower extremities.

In our case, no pulsation could be seen in the veins of the ocular

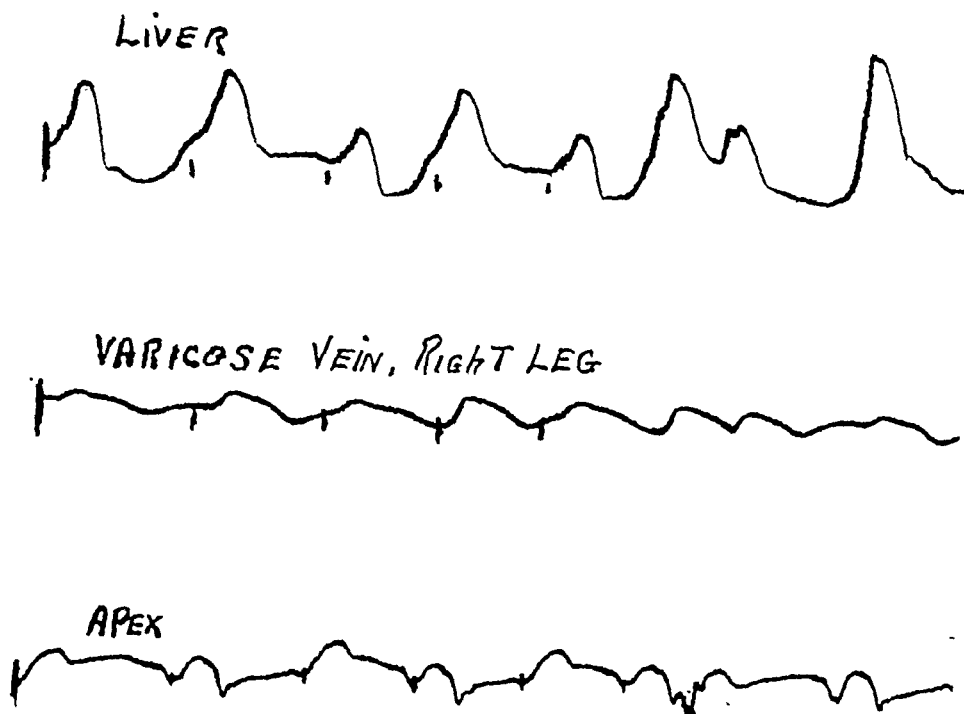


Fig. 3.—Polygraphic tracing made from the apex beat, the liver, and the varicose vein of the right leg.

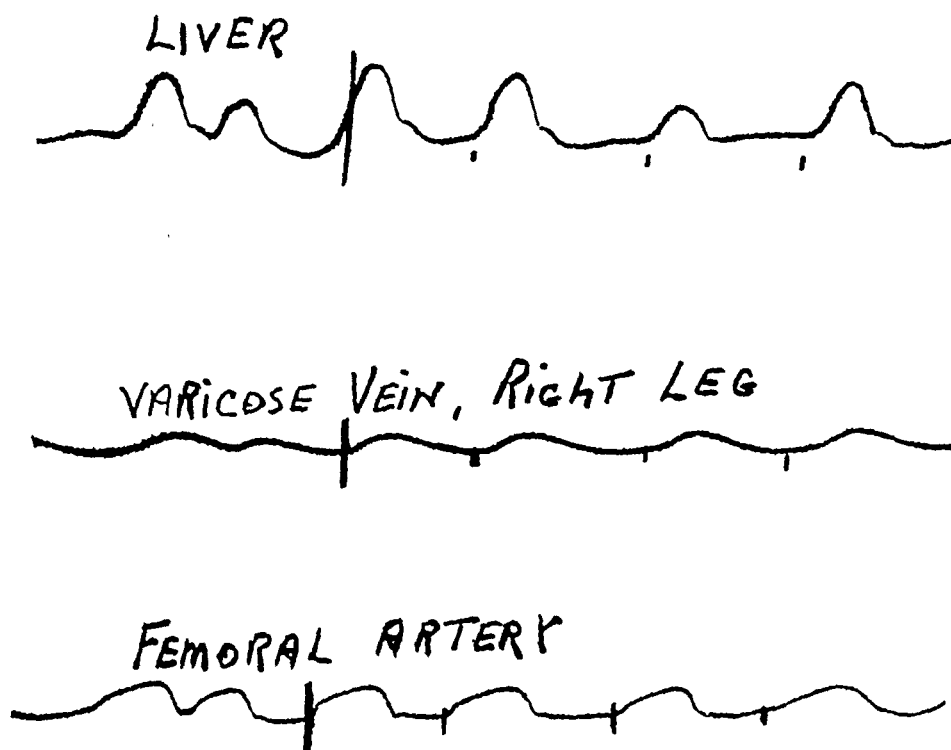


Fig. 4.—Polygraphic tracings from the femoral artery, varicose vein of right leg, and the liver. The large vertical lines on the left of each tracing indicate the starting positions of the writing pens.

fundi, and there were but slight visible pulsations of the distended veins of the arms. However, there were marked and vigorous pulsations of the cervical veins and in the varicose veins of both legs. The pulsation of the liver could be seen from a distance of several feet.

Polygraphic tracings were made from the cardiac apex, carotid artery, jugular vein, liver, femoral artery, and the varicose veins of the leg. The liver and leg vein pulses were found to correspond with the apex beat, and there was a similar relationship between the pulsation in the

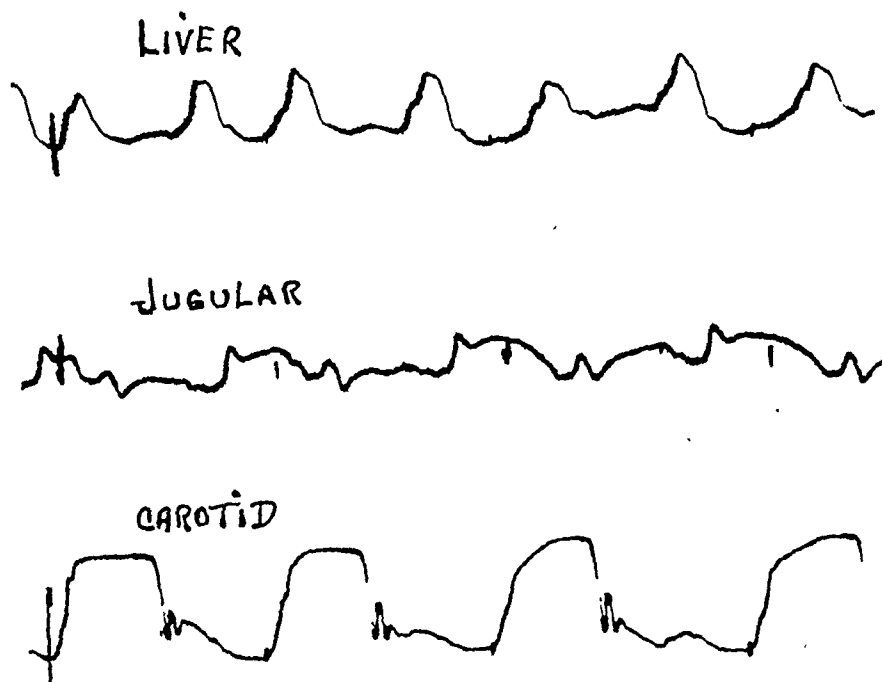


Fig. 5.—Polygraphic tracings from the carotid artery, jugular vein, and liver, showing a 2:1 ratio of the arterial and venous pulsations.

liver and leg veins and that in the femoral artery (Figs. 3 and 4). The temporal relations of the apex beat and liver and venous pulses varied slightly, but this was thought to be an artifact. The conclusion was drawn that the ventricular contractions originated the venous deflections.

In one record, on which, unfortunately, no apex tracing was made, the liver and carotid pulses had a 2 to 1 ratio (Fig. 5). This was interpreted as meaning that, at that time, the insufficiency of the tricuspid valve and the force of the ventricular beat were such that complete regurgitation through the incompetent tricuspid valve, rather than opening of the aortic valve and ejection into the aorta, occurred every second beat. Subsequent tracings failed to show this phenomenon; instead, there was always a 1 to 1 ratio of the apex, carotid, and liver pulsations. In a few tracings from the jugular vein, small deflections preceding what appeared to be C waves were noted. However, they were never clear

enough or large enough to be definitely called waves, and no clear evidence of auricular activity was ever obtained.

The venous pressure in the antecubital and femoral veins was always elevated, even after the cardiac status of the patient had improved and she had become free of peripheral edema and gross pulmonary congestion. Likewise, the circulation times were persistently prolonged, although the arm-to-lung circulation time was but moderately increased as compared with the arm-to-tongue time; the latter was consistently 2 to 3 times larger than normal. This was surprising, in view of the outstanding evidence that the heart failure was predominantly right-sided.

CONCLUSION

A case of tricuspid insufficiency with venous pulsation in the neck, a markedly pulsating liver, and pulsation in varicose veins of the legs is presented.

We are indebted to Dr. E. J. Leopold, of Sinai Hospital, Baltimore, Maryland, for permission to examine the records of this patient's admission to that hospital. Dr. C. McC. Brooks, of the Physiology Department of the Johns Hopkins Medical School, was kind enough to interpret the polygrams.

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ENDOCARDITIS CAUSED BY THE *MICROCOCOCCUS PHARYNGIS* SICCUS: RECOVERY AFTER TREATMENT WITH HEPARIN AND SULFAPYRIDINE

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ENDOCARDITIS caused by the *Micrococcus pharyngis siccus*, which is ordinarily a nonpathogenic inhabitant of the upper respiratory tract of man, has been reported four times.¹⁻⁴ Endocarditis caused by closely related organisms which may be indistinguishable bacteriologically⁵ from the *Micrococcus pharyngis siccus* is also rare; one case of *Micrococcus catarrhalis* endocarditis,⁶ two cases of *Micrococcus pharyngis flavus* endocarditis,^{7, 8} and two cases of endocarditis caused by similar, but not identical, Gram-negative cocci^{9, 10} have been reported.

We are reporting an additional case of endocarditis caused by the *Micrococcus pharyngis siccus*. This patient, unlike any previously reported, is apparently cured. One year after her acute illness she was alive and well. Recovery occurred during November, 1940, while heparin and sulfapyridine therapy was being employed. The clinical diagnosis was based upon the following evidence: (1) multiple embolic phenomena, manifested by meningitis, attacks of acute, left-sided, upper abdominal pain, occasional erythrocytes in the urine, crops of white-centered petechiae involving the mucous membranes, retinae, and finger tips; (2) a changing heart murmur; (3) two positive blood cultures for *Micrococcus pharyngis siccus* before treatment was begun; and (4) the absence of a demonstrable focus for emboli other than the heart.

CASE REPORT

H. J. (X-15339), a 14-year-old, colored schoolgirl, was admitted to the Detroit Receiving Hospital Oct. 16, 1940, in an irrational and semiconscious condition.

The patient had apparently been well until Sept. 28, 1940, eighteen days before her admission to the hospital, when, on the last day of her menstrual period, she developed a dull, frontal headache and felt feverish. These symptoms were attributed to playing too long in the sun without a hat. The headache persisted, and radiated from behind the left eye across the forehead and to the vertex. On the second day of her illness blurring of vision appeared. After she had been ill about a week without improvement, she was seen by a physician. He reported a temperature of 103° F., diagnosed "acute sinusitis," and advised rest in bed.

During the second week, the patient's condition grew worse. Her headache became more severe, the blurring of vision was more marked, and her neck became stiff. She continued feverish, and, for five or six days, vomited all solid food, and most liquids. Finally she became semistuporous and irrational. She was again seen by a physician, who sent her into the hospital.

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92 per cent neutrophiles; the hemoglobin was 10 Gm. The blood Kline reaction was negative. On lumbar puncture, the initial pressure was 260 mm. of water. The spinal fluid was turbid, and contained a slight trace of globulin. The spinal fluid cell count showed 265 leucocytes, of which 95 per cent were neutrophiles; the Kline reaction was positive, and the dextrose content was 76 mg. per cent. No organisms were found on direct smear of the sediment, and culture was negative. Roentgenograms of the chest and paranasal sinuses were negative.

Bacteriologic Studies.—Blood cultures which were taken on the day of admission and two days later yielded a Gram-negative, bean-shaped diplococcus after about forty-eight hours' incubation. On blood agar the colonies appeared dry and grayish, and crumbled when removed. Agglutination tests with antimeningococcus serum were negative. Spontaneous agglutination occurred in physiologic saline solution. In fermentation tests, the organisms produced acid in dextrose, levulose, maltose, and sucrose, with no reaction in lactose, galactose, inulin, mannitol, and dulcitol. Because of these observations the organism was identified as *Micrococcus pharyngis siccus* in our laboratories, and this identification was confirmed by the laboratories of the Michigan State Health Department.

Course and treatment are charted in Fig. 1.

Sulfapyridine was begun on the second hospital day with an initial dose of 5 Gm. This drug was administered thereafter in doses of 4 to 6 Gm. daily from October 20 to November 22, save for three days when it was stopped because of a mistaken fear that it might be playing a role in the patient's rapidly increasing anemia. One-sixth of the daily dose (0.6 to 1.0 Gm.) was given every four hours, day and night. The blood level was maintained between 4.6 and 9.6 mg. per 100 c.c. during this thirty-three-day period. On the day after the first administration of sulfapyridine the blood cultures became negative, and they remained negative thereafter.* On the second day, the temperature fell to normal, but, after a chill, it became septic again within thirty-six hours.

The patient continued critically ill, and had a rapidly increasing anemia, so that transfusion was required. Almost every day new hemorrhages and white-centered petechiae appeared in the conjunctivae, retinae, or mucous membranes. One day a transient paralysis of the left external rectus oculi was demonstrated; there were two sudden attacks of left upper quadrant pain, associated with vomiting, and occasionally the urine showed erythrocytes. The apical systolic murmur became harsher. The electrocardiogram, which was normal on admission, showed transient inversion of the T wave in Lead I and transient flattening of the T wave in Lead IV-F. The patient's neck remained stiff, and another lumbar puncture showed pleocytosis, increased globulin, and a positive Kline reaction.

On November 1, the thirty-third day of her illness, and eleven days after sulfapyridine was begun, a supply of heparin was obtained, and an initial dose of 20,000 units of Liquaemin† was given intravenously. From November 1 until November 21, in order to maintain the coagulation time at about fifteen minutes by Lee and White's three-tube technique, 20,000 to 80,000 units of heparin, diluted with saline, were given intravenously daily. The average daily dose was about 40,000 units. Sulfapyridine was continued.

During two weeks of this combined therapy, the patient continued acutely ill. New petechiae were noted on November 5, 8, and 13. On the fifteenth day of combined treatment, she began to improve; her neck became less stiff, her headache disappeared, she became cooperative, and her temperature fell to normal. Seven days later, after three weeks of combined heparin-sulfapyridine therapy, medication was discontinued. Further recovery was uneventful.

*At this time, sodium para-aminobenzoate was not used in our blood-culture media.
†Liquaemin, a brand of heparin, was kindly supplied by the Hoffman-LaRoche Co.

TABLE I
PRINCIPAL CLINICAL FEATURES IN FIVE CASES OF *Micrococcus pharyngis sicca* ENDOCARDITIS

	AGE	COLOR	SEX	ONSET	PREVIOUS HEART DISEASE	HEART SIZE	HEART MURMURS	EMBOLIC MANIFESTATIONS				BLOOD CULTURE	LEUCOCYTE COUNT	DURATION ILLNESS (DAYS)
								PETECCHIAE	MENINGEAL (SPINAL FLUID)	PALPABLE SPLEEN	HEMATURIA			
Schultz ¹ (1918)	25	W	M	Sudden, with headache, fever, generalized aching	None	Normal	Rough, apical systolic, transmitted to axilla	Skin, mucous membranes, serosal surfaces	Irrational, C.S.F.: "pus and globulin"	Yes (about 500 Gm.)	Occasional	2 pos.	18,000 to 19,200	18*
Grace, et al. ² (1932)	27	W	M	Sudden, with cramping lower abdominal pain, painful fingers and toes	Rheumatic, with mitral stenosis and insufficiency and nor-	Enlarged (945 Gm.)	Systolic and diastolic murmurs at both apex and base	Skin, mucous membranes, serosal surfaces, 2 Osler nodes	None	No (699 Gm.)	RBC increase in Addis count	1 pos.	Not reported	20*
Goldschmidt ³ (1934)	21	W	F	Sudden, with headache, chills and fever, generalized aching	Rheumatic, with mitral stenosis	Normal (300 Gm.)	Diastolic rumble at apex	Skin over chest	Stiff neck C.S.F.: 450 WBC, 98% PMN's Culture +	No (350 Gm.)	None	1 pos.	26,000	14*
Shilling ⁴ (1939)	26	W	M	Chills and fever for six weeks	None	Normal (350 Gm.)	Rough, apical systolic, transmitted to axilla	None; embolic occlusion of right brachial and femoral arteries	None	No (207 Gm.)	Frequent	"Many" pos.	16,000	91*
IL. J. (Now ense)	14	B	F	Sudden, with headache, fever, blurred vision	None known	Normal (x-ray)	Rough, apical systolic, transmitted to axilla	Mucous membranes, retino, skin	Stiff neck; Kernig + C.S.F.: 265 WBC, 95% PMN's Culture -	No	Occasional	2 pos.	29,000 to 37,200	49

*Illness terminated in death. Diagnosis proved by post-mortem examination.

She has remained well for one year. Examination on Nov. 14, 1941, revealed a well-developed and well-nourished girl who was apparently in good health. The temperature was 98° F., the pulse rate, 80, the respiratory rate, 20, the blood pressure, 118/80, and the weight, 103 pounds (a gain of 32 pounds during the year). Vision was 20/40 O.D., and 20/100 O.S.; this was correctible to 20/30 in both eyes. There was a whitish macular lesion in the right eye which had fairly sharply defined edges, and several small pigmented spots were seen about the macula of the left eye. Several small pigmented areas were also present on the soft palate. The heart was of normal size, but, roentgenographically, there was a slight increase in the left auricular curve. At the apex there was a rough systolic murmur, transmitted to the axilla, but no diastolic murmur was heard. The pulmonic second sound was accentuated and split. Neurologic examination was negative. Laboratory studies, including a blood culture and an electrocardiogram, showed nothing abnormal.

DISCUSSION

A review of all the reported cases of *Micrococcus pharyngis siccus* endocarditis is of some interest (Table I). The patients' ages ranged from 14 to 27 years. There were three males and two females. The onset of the disease was uniformly sudden, with headaches, chills, fever, and general malaise. Other symptoms depended upon the areas affected by emboli. In two instances, the site of the cardiac lesion was an otherwise normal mitral valve; in two, valves previously damaged by rheumatism were affected. All of the patients had rough cardiac murmurs, all had striking embolic manifestations, namely, petechiae, splinter hemorrhages under the nails, splenic infarcts, and renal infarcts, and three had meningeal involvement. All had a considerable leucocytosis, ranging from 16,000 to 37,000. The course of the illness was acute in three cases, in which death occurred on the fourteenth, eighteenth, and twentieth day, respectively, after onset. One patient lived thirteen weeks, and one, with meningeal involvement, who was treated with heparin and sulfapyridine, is apparently cured.

SUMMARY

A case of *Micrococcus pharyngis siccus* endocarditis is reported. This patient, who was acutely ill, and had meningeal involvement, multiple white-centered petechiae, occasional hematuria, and changing cardiac murmur, was treated with heparin and sulfapyridine, and recovered; she has remained well for one year.

Four other previously reported cases are reviewed.

ADDENDUM

The patient was in good health when re-examined in February, 1943. The cardiac signs were similar to those of Nov. 14, 1941.

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10. Dammin, G. J.: Subacute Bacterial Endocarditis Caused by a Hitherto Undescribed Gram-Negative Coccus, *Ann. Int. Med.* 15: 756, 1941.

Correspondence

TO THE EDITOR:

Our attention has just been called to the article by Patterson, Clark, and Levy, entitled "A Comparison of Electrocardiographic Changes Observed During the Anoxemia Test on Normal Persons and on Patients With Coronary Sclerosis," which appeared in the *AMERICAN HEART JOURNAL*, June, 1942, p. 837, and to the appended criticism of a paper by Burnett, Nims, and Josephson on the same subject in an earlier issue of the same journal. We have followed closely the work of the Colorado group, and, in our opinion, an analysis of the various articles published by Levy and his coworkers will support the unfavorable view of this test taken by Burnett and his group.

The method followed by Levy in the development of his criteria has evidently consisted of subjecting a group of persons who are normal with respect to their coronary circulation to the anoxemia test, and regarding all of the responses encountered as negative. Through the device of repeatedly revising their previously published electrocardiographic criteria for coronary inadequacy, they are now able to present data which show that all normal persons in their series exhibit a negative response. But this otherwise desirable feature of their test has been obtained at the expense of very largely destroying its ability to uncover hidden or subclinical coronary insufficiency, and of seriously diminishing the percentage of abnormal persons who respond with a positive reaction. Indeed, in their latest paper, only 49 per cent of the patients on whom the Levy group had made the clinical diagnosis of coronary sclerosis were positive reactors. Under these conditions, it seems pertinent to ask how much additional information a clinician may expect to get from the Levy test, in as much as the criteria make it unlikely that subclinical coronary insufficiency will be revealed, and, further, will, as like as not, provide a false negative response when the clinical observations point clearly to coronary sclerosis. On the other hand, any attempt to increase the percentage of positive reactors among the abnormal subjects by increasing somewhat the anoxic stress will result, as the Burnett group have shown, in a substantial number of false positive reactors among the normal subjects.

The present unsatisfactory state of the Levy test is, in our opinion, due largely to two uncontrolled factors. The test, as now employed, is apparently not a direct measure of the status of the coronary circulation, but rather of myocardial anoxemia. The development of myocardial anoxemia under stress, however, is the net result of interaction between the coronary circulation and a complex of compensatory re-

actions. A person with a normal coronary circulation may thus react as a false positive because of a deficiency in these compensatory reactions, or, conversely, unusually efficient compensatory reactions may produce a false negative reaction in a person who has a moderate degree of coronary insufficiency. In other words, the degree of myocardial anoxemia, and, hence, the electrocardiographic response, does not necessarily reflect the condition of the coronary vessels. Another unfortunate feature of the Levy test is the fact that the criteria are based primarily upon the clinical diagnosis. As is well known, the clinical diagnosis of coronary sufficiency or insufficiency is uncertain. In fact, it was this uncertainty which led the Levy group to attempt the development of a test. As long as the present criteria are used, therefore, the Levy test can hardly be expected to add much to the accuracy of clinical diagnosis. The conclusion seems justified that some more secure foundation for the criteria must be found. Perhaps this will require the laborious correlation of the results of repeated tests with numerous and prolonged clinical observations, together with an analysis of the state of the vessels post mortem. A tremendous task!

Another important point at which we are in disagreement with the Levy group is the question of safety. These workers have, themselves, reported three instances of pulmonary edema and one of shock during the course of anoxemic stress. Although it is now recommended that no one should be subjected to the test twice in twenty-four hours, does not their own experience indicate that there is a definite hazard?

These criticisms of the Levy test are not made without a due appreciation of the very great difficulties inherent in the task which they have undertaken. It is rather our wish to give expression to our belief that the test, as yet, has not been developed sufficiently to warrant recommending its general adoption by the profession at large.

RICHARD W. WHITEHEAD
WILLIAM B. DRAPER
Denver, Colo.

TO THE EDITOR:

With the final conclusion of Whitehead and Draper I am in complete agreement, namely, that the time has not come when the anoxemia test should be recommended for general use. It certainly should not be employed by those who do not understand the principles upon which it is based and who are unable to carry out the directions which have been given for its performance.

The answers to most of the questions raised are to be found in papers published by my collaborators and myself, as well as in the addendum to the article which appeared in the *AMERICAN HEART JOURNAL* for June, 1942, p. 837. For the sake of clarity, I will recapitulate, and also cite some of the experiences of others who have used this procedure.

1. Criteria for the normal response obviously must be obtained from persons who present no clinical evidence of cardiac disease. Such normals do not die within a short time, so that the heart cannot be examined directly.

2. The test was electrocardiographically positive in 49 per cent of 157 cases of coronary sclerosis, and furnished presumptive evidence of coronary insufficiency, by the occurrence of pain, in another 20 per cent. It was thus helpful in the recognition of a diminished coronary reserve in 69 per cent. The importance of the occurrence of pain during the test has been fully discussed (*J. A. M. A.* 117: 2113, 1941). Gilbert and his associates have used this method of induced anoxemia to study the effects of various drugs upon patients with angina of effort, depending solely upon the appearance of pain as an end point (references in paper cited above).

3. Individual case histories have been given in detail to indicate how the test may aid in diagnosis in doubtful cases. In a small number, postmortem examination has confirmed the results of the test. Serial observations over a period of years have already been reported.

4. Neither Burnett nor his colleagues are in a position to speak of the safety of the test, or, rather, of its dangers. They worked with a 10 per cent oxygen mixture at an elevation of 5,000 feet, which means that the patients actually breathed the equivalent of an 8 per cent mixture. In addition, in at least six cases, through error, Burnett used a mixture containing 8.6 per cent, so that these subjects inhaled about 7 per cent oxygen. As previously stated, because of the conditions of the Denver experiments, the results are not comparable to ours, and the conclusions drawn do not apply to the anoxemia test which we have described.

5. In the earlier period of our work several unpleasant reactions occurred. The test has now been made in our laboratory almost 2,000 times. We have advised that three precautions be observed. Only the first of these is mentioned by Whitehead and Draper, namely, that the test should not be performed more than once in twenty-four hours. In addition, we have urged that it should not be carried out in the presence of congestive heart failure or within four months of known cardiac infarction. If these directions are followed, serious reactions may be avoided.

6. The electrocardiographic response does not necessarily reflect the condition of the coronary arteries; we have specifically stated that "it yields no information as to the nature or extent of the pathologic lesions in the heart." But it does serve as an index of the coronary reserve, and, hence, of the adequacy of the coronary blood flow. As in all functional tests, there must be a significant diminution in reserve before a positive result is obtained.

A number of reports on the use of the anoxemia test have been made. Among them are the following:

Dr. Arlie R. Barnes, Mayo Clinic, Rochester, Minn. (Proc. Staff Meet., Mayo Clin. 17: 316, 1942). The test was carried out on a patient "who was thought to have coronary sclerosis and who presented atypical symptoms of angina pectoris." After describing the changes observed in the electrocardiograms, which are reproduced, Barnes states: "I consider, therefore, that these changes are of sufficient degree and of a quality to confirm strongly the clinical suspicion that this patient had coronary insufficiency. On comparing the tracings before and during anoxia in a similar case in which the same question arose, depressions of the S-T segments were noted in Leads I, II, and IV-R. There seems little doubt that such changes are indicative of severe coronary insufficiency."

Dr. Harold J. Stewart, New York City (Letter). "We have been using your anoxemia test for fifteen months or so in my Sub-Department of Cardiology at the New York Hospital and Cornell University Medical College. We wished to accumulate data and form an impression from our own experience about the value of the test. We have been careful in adhering to the methods which you have devised and your technique. For six months we were running a fair number of tests, but in the last six months, because of staff shortage, I have had to limit the number to those requested rather than seeking cases to do. We have run seventy-five tests so far.

"1. We have had no difficulties in doing the test and no untoward effects have been encountered. We have kept in mind those cases in which you have advised against its use and the reasons for discontinuing a test.

"2. We did the test first in a certain number of normal individuals to get the feel of the test, setting of routine, etc.

"3. We have used your criteria in analyzing the results.

"4. We have done the test in certain types of patients. Our results have not been analyzed, but I have the following impressions:

"a. In those in whom clinically the symptoms appeared to be angina in order to see how the correlation fitted in them, it seems that either significant electrocardiographic changes or pain typical of their spontaneous attacks or both may occur with breathing of low O_2 .

"b. Those with unusual distribution or occurrence of pain in which the question of angina could not be decided clinically, in which there might or might not be any electrocardiographic changes indicating coronary artery changes, and in which objective help was needed: In about half of these the test was positive and in about half negative.

"c. Those who did not from history, etc., appear to have angina and the facts in the examination and the laboratory data did not point to cardiac damage, but who thought they had angina: In most of these the test has been negative.

"I think that it is a useful test, and as my experience with it increases. I get more confidence in how to accept the results. I still want to see

the patient myself and make the clinical estimate of the pain and then see how it links up with the test. If an objective test parallels the clinical findings frequently enough, both in a negative and a positive way (i.e., typical angina and normals) it seems justifiable to go from the positive or negative test to the clinical interpretation, and as time goes on and more of the cases come to autopsy, the basis will be more clearly established, as you all too well emphasize. It may take putting together the experience of many investigators over years to make this latter correlation. I think you have been extremely careful in your claims for the test and have not stepped beyond the bounds of the content of your data in your own estimate of it."

Dr. Harold Feil, Lakeside Hospital, Cleveland, Ohio (Letter). "My results with the anoxemia test have been very satisfactory, and judging from clinical criteria there were no false positives. In one case the chest lead was more strongly positive than the exercise test. It is a diagnostic help in border-line cases, and parallels much the changes in the exercise test."

Dr. Nelson G. Russell, University of Buffalo, Buffalo, N. Y. (Letter). Dr. Russell kindly sent me full clinical notes and the autopsy protocol of a man, 51 years old, who gave a history of distress in the chest on exertion which came on after walking three or four blocks. The electrocardiogram showed no definite abnormality. The anoxemia test was positive, and pain appeared six minutes after the inhalation of 10 per cent oxygen was begun. The patient died suddenly one year and eleven months after the test was made. Examination of the heart at autopsy showed no cardiac enlargement. There was advanced atherosclerosis of all of the coronary arteries. The left was almost entirely occluded at its exit from the aorta, and the narrowed lumen contained a recent clot. The anterior descending branch was completely filled with an older, organized thrombus. The circumflex branch of the left coronary showed a thickened wall and moderate narrowing of its lumen. The right coronary was diffusely atherosclerotic, but its lumen was patent. No recent infarcts were present.

S. A. Thompson and M. J. Raisbeck, New York City (Ann. Int. Med. 16: 495, 1942). These observers used induced anoxemia in studying patients prior to cardio-pericardiopexy. They describe the criteria of a positive test, and state: "We have considered such changes as evidence of a subnormal coronary blood supply." The electrocardiograms illustrating the test in three of their patients are published. They add: "In no cases have we observed the development of alarming symptoms or more than transient distress."

It is our hope that further studies will extend these observations and furnish additional evidence of the usefulness of the method.

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New York, N. Y.

Abstracts and Reviews

Selected Abstracts

Kiely, W. F., Hamilton, S. L., and Gellhorn, E.: The Influence of Hemorrhage on Skeletal Muscle Tone. *Am. J. Physiol.* 137: 251, 1942.

Hemorrhage leads in unanesthetized, decerebrate dogs to a rise in muscle tone which is reversed on reinfusion of the blood.

Adrenalin raises blood pressure and muscle tone but ephedrine is without effect on the muscle tone in concentrations which have a decided pressor effect.

Hemorrhage causes a rise in muscle tone even when a fall in blood pressure is prevented by simultaneous injection of ephedrine.

Bilateral denervation of the carotid sinus area does not prevent the rise in muscle tone during hemorrhage.

AUTHORS.

Calabresi, M., and Geiger, A. J.: Potential Changes in Injured Cardiac Muscle. *Am. J. Physiol.* 137: 440, 1942.

Evidence obtained both electrographically and by means of a suitable micro-voltmeter indicates that the surface of an area of injury in the beating heart is the site of important changes in electrical activity during systole, and that the monophasic electrogram obtained from the injured heart results predominantly from potential changes at the electrode over the injured area. The authors' observations therefore stand in opposition to the traditional view in this regard, and they confirm the stand recently taken by several others.

AUTHORS.

Shuler, R. H., Ensor, C., Gunning, R. E., Moss, W. G., Johnson, V.: The Differential Effects of Respiration on the Left and Right Ventricles. *Am. J. Physiol.* 137: 620, 1942.

In dogs anesthetized by sodium barbital, direct cardiac volume changes were measured by means of an oncometer during normal breathing, with the ventricles exposed to intrathoracic pressure changes. During inspiration there was an increase in total diastolic size and stroke volume of the two ventricles. This confirms the findings of Boyd and Patras (1941).

Systemic arterial pressure decreased during inspiration in spite of increased total cardiac output during the same phase of respiration.

Under sodium barbital anesthesia, a portion of the ventral chest wall was removed, the heart exposed, and paper markers affixed to the heart so as to outline each ventricle. A window was sealed into the ventral chest opening, normal respiration was reinstated, and motion pictures were taken of the heart. Successive single frames were projected, the area of each ventricle measured in each frame, and these areas plotted together with simultaneous intrathoracic and carotid pressures. The right ventricle showed increased diastolic size and stroke volume during inspiration, while the same measurements on the left ventricle decreased; the reverse was true during expiration.

The increased diastolic size and stroke of the right ventricle during inspiration suggest that more blood is pumped into the lungs during that phase, while the decreased diastolic size and stroke of the left ventricle indicate that the blood is withheld from the left side of the heart until the onset of expiration.

Systemic arterial blood pressure measurements on trained, unanesthetized dogs showed but slight reduction of respiratory influences on blood pressure when intrathoracic pressure influences were eliminated by the use of a differential manometer. These reductions are equivalent to simultaneous intrathoracic pressures, but are not sufficient to eliminate respiratory fluctuations in blood pressure.

The main factor responsible for the arterial blood pressure fluctuations of respiration is the changing output of the left ventricle. A sinus arrhythmia and direct influences of intrathoracic pressures may modify somewhat these blood pressure changes.

Each ventricle responds independently in accordance with the Starling principle, regardless of the diastolic size of the other ventricle.

AUTHORS.

Woodbury, R. A., and Robertson, G. G.: The One Ventricle Pump and the Pulmonary Arterial Pressure of the Turtle: The Influence of Artificial Acceleration of the Heart, Changes in Temperature, Hemorrhage and Epinephrine. *Am. J. Physiol.* 137: 628, 1942.

The right and left aortic pressure pulses of turtles are synchronous and show equal pressures. Blood flow and the systolic pressure rise occurs slightly earlier in the pulmonary artery than in the aorta. During the last part of systole the pulmonary pressure becomes 2 or more mm. Hg below that in the aorta. During diastole the pulmonary pressure descends more rapidly and to a lower value than that in the aorta.

No evidence was obtained that the ventricle retains any significant residual volume of blood at the end of the ejection period. The cardiac output in turtles is increased by an increased heart rate and/or an increased diastolic filling of the ventricle.

Cooling or warming the turtle respectively lowers or elevates the pulmonary systolic and diastolic pressure. At body temperatures near 0° C., diastole is excessively prolonged. This is vagal in origin.

The presence of only one ventricle enables the turtle to regulate effectively the distribution of blood flow between the systemic and pulmonary areas. If the need arises (after hemorrhage) blood flow can be diverted into the systemic vessels by closing off the orifice of the pulmonary artery during the greater part of systole and by reducing the size of the pulmonary arterial reservoir.

Epinephrine HCl administered intravascularly increased the peripheral resistance of the systemic vessels, increased the muscle tone of the great pulmonary arteries, but gave no evidence of any effect upon the peripheral resistance of the pulmonary circulation.

AUTHORS.

Warren, J. V., Walter, C. W., Romano, J., and Stead, E. A., Jr.: Blood Flow in the Hand and Forearm After Paravertebral Block of the Sympathetic Ganglia. Evidence Against Sympathetic Vasodilator Nerves in the Extremities of Man. *J. Clin. Investigation.* 21: 665, 1942.

On two occasions, the sympathetic ganglia supplying the right upper extremity of a normal subject were injected with novocain by the paravertebral route. The blood flow in the hand and forearm was measured before, during, and after the anesthetization.

Complete absence of any vasomotor activity in response to sensory stimuli or deep inspiration indicated complete paralysis of the sympathetic ganglia supplying the right hand. The sympathetic paralysis produced a striking increase in blood flow. After the effect of novocain had passed away the right hand was immersed in water at a temperature of 43° C. Local heat produced the same increase in blood flow in the right hand as had sympathetic paralysis.

The fact that complete blocking of sympathetic ganglia produces full vaso dilatation in the hand demonstrates that inhibition of sympathetic activity is sufficient to explain the vasodilatation which occurs in the hand when the body is heated. There is no necessity for postulating that the sympathetic nerves to the hand contain vasodilator fibers.

In the forearm, paravertebral novocainization of the sympathetic ganglia caused a six-fold increase in blood flow. A similar increase in blood flow was produced by immersing the forearm in hot water (46° C.). This indicates that removal of all sympathetic impulses to the vessels of the forearm produces as great a rise in blood flow as does heating the part. Inhibition of vasoconstriction adequately explains the increase in blood flow which occurs when the body is heated, and there is no need to assume that the sympathetic nerves to the forearm contain vasodilator fibers.

The fact that neither heating the forearm nor injection of the sympathetic ganglia with novocain produces maximal dilatation in the forearm indicates that many of the vessels of the forearm are not under control of the sympathetic nervous system. It is suggested that the vessels of the skin of the forearm are under the control of the sympathetic nervous system, and that those of the muscle are not.

AUTHORS.

Swank, R. L., and Bessey, O. A.: Production and Study of Cardiac Failure in Thiamine-Deficient Pigeons. Arch. Int. Med. 70: 763, 1942.

A chronic deficiency of thiamine without starvation will produce signs of cardiac failure in pigeons.

This is preceded and accompanied by tachycardia and electrocardiographic abnormalities.

Necrosis of myocardial fibers with inflammatory cell infiltration occurs frequently, although late, in thiamine-deficient pigeons.

The electrocardiographic abnormalities and evidences of cardiac failure in thiamine-deficient pigeons are accompanied by marked decrease in the cocarboxylase content of the heart muscle.

The electrocardiographic abnormalities and the evidence of cardiac failure, if not too severe, respond immediately to treatment either with thiamine hydrochloride or cocarboxylase.

Starvation alone or during thiamine deficiency produces bradycardia and frequently variable heart block in pigeons.

The methods and mechanism by which tachycardia and evidences of cardiac failure are produced in thiamine deficiency are presented and discussed. It is suggested that the tachycardia is due to vasodilatation, which is caused by the local accumulation of intermediate products of carbohydrate metabolism. This also facilitates transudation of fluid from blood vessels to form hydropericardium and other evidences of cardiac failure. In addition, thiamine deficiency impairs the function of the heart, increases the tendency to extravascular fluid collections and results in terminal cardiac standstill. It seems probable that thiamine deficiency, in the absence of peripheral vasodilatation, causes bradycardia, but unfortunately most experiments involving such deficiency have been complicated by marked starvation, which also is known to cause bradycardia.

AUTHORS.

Zeek, P. M.: Heart Weight. I. The Weight of the Normal Human Heart. Arch. Path. 34: 820, 1942.

Statistical analysis of the weights of hearts from 926 adult bodies in which was found no clinical or pathologic evidence of heart disease or of any commonly recognized cause of myocardial hypertrophy revealed the following factors to have an effect on heart weight: sex, body length and state of body nourishment. No effect of age or race on heart weight was demonstrated.

In relatively normally nourished males the weight in grams of a normal heart was found to be $1.9 \text{ B. L.} - 2.1 \pm 40$, B. L. being the body length in centimeters. The normal heart weight in normally nourished females was found to be $1.78 \text{ B. L.} - 21.58 \pm 30$. Since emaciation and obesity are parts of pathologic processes, the variations in heart weights found to be associated with these conditions were considered departures from normal. Therefore, bodies presenting these conditions were not included in the series used for the determination of standards for normal heart weight. These standards based on body length were found to be more accurate and more useful than the commonly employed standards related to body weight.

AUTHOR.

Schleser, I. H., and Langendorf: The Significance of the So-Called P-Pulmonale Pattern in the Electrocardiogram. Am. J. M. Sc. 204: 725, 1942.

The P-pulmonale pattern is not pathognomonic of chronic pulmonary disease, since it occurs in its absence, as it appears in a variety of other conditions.

P-pulmonale in association with low "voltage" in the limb leads or with right ventricular preponderance represents the characteristic electrocardiogram of chronic cor pulmonale.

It is of diagnostic importance to distinguish the P-pulmonale pattern from that seen in rheumatic mitral stenosis. The P-wave pattern can be used as a diagnostic hint in determining the cause of right ventricular preponderance if both are found in the same record.

Further anatomic and roentgen ray correlation studies are necessary to establish definitely whether P-pulmonale is due to altered position, increased strain on, or hypertrophy of the right auricle.

AUTHORS.

Burchell, H. B.: Observations on Additional Instances of a Supernormal Phase in the Human Heart. J. Lab. & Clin. Med. 28: 7, 1942.

The presence of the supernormal period in the human heart has been used to explain cases of *interference dissociation* in which the auricles are beating more rapidly than the ventricles, cases of *paroxysmal heart block* in which cessation and resumption of auriculoventricular conduction have a phasic dependency on the immediately preceding electrical events and cases of *possible parasystolic rhythm*. An example is given of each of the first two types of mechanism which are best explained by the existence of a supernormal period in excitability of the conduction tissues. Case 2 is considered of some importance, as it is another instance of the undoubtedly rare cases in which the supernormal period has played a role in the maintenance of normal sinus rhythm. Following establishment of complete block, the patient has remained in relatively good health for two years.

AUTHOR.

Miller, J. R., and Dent, R. F.: A New Hypothesis of the Production of the T Wave in the Electrocardiogram Based on Electrokinetic Phenomena. *J. Lab. & Clin. Med.* 28: 168, 1942.

The nature of the T wave in the electrocardiogram suggests that it is due to an electrokinetic cause and does not represent retreat electric disturbances. The structure of the heart with its capillary bed is such that contraction could produce streaming potentials of the order of magnitude of the T waves. Pressure perfusion of the heart showed this to be entirely possible. Constriction of the unresponsive heart likewise produced this phenomenon. In addition it is shown that the T wave corresponds in time to the increase in pressure in the left ventricle. These observations suggest that contraction of the heart with its resultant streaming potentials is responsible for the T wave in the electrocardiogram.

AUTHORS.

Richardson, J. S.: Chest Leads in Congenital and Acquired Dextrocardia. *Brit. Heart J.* 4: 80, 1942.

Two cases of congenital dextrocardia with transposition of the viscera were found to have in chest leads, T waves that had deflections in the opposite direction from the normal.

In two cases of acquired dextrocardia, one had T waves in leads, taken from the right side of the chest, that resembled those of congenital dextrocardia in direction, but the other conformed to the tracing found in about 20 per cent of subjects with normally placed hearts.

AUTHOR.

Abbott, G. A., and Russek, H. I.: Calcareous Aortic Stenosis in a Case of Dextrocardia With Situs Inversus. *Am. J. M. Sc.* 204: 516, 1942.

A case is presented in which calcareous aortic stenosis (rheumatic?) was found in a 43-year-old male with situs inversus. Electrocardiograms showed the effect of the conditions cited. There is no evidence of a similar case having been reported.

AUTHORS.

Abramson, D. I., Fierst, S. M., and Flachs, K.: Effect of Muscular Exercise Upon the Peripheral Circulation in Patients With Valvular Heart Disease. *J. Clin. Investigation* 21: 747, 1942.

Using the venous occlusion plethysmographic method, the rate of resting peripheral blood flow and the circulatory response to exercise were studied in a series of 29 patients with insufficiency of the aortic semilunar valves, and in 16 subjects with mitral valvular disease.

The average circulation in the hand was found to be somewhat diminished in both series of patients as compared with that for the control series, while the readings in the forearm and leg in the majority of the cases fell within the normal range.

The post-exercise response of the blood vessels in the forearm to a specified amount of work was generally greater than that in the control group.

It was concluded that, in the majority of the patients with aortic insufficiency or mitral valvular disease, no evidence was found to indicate that excessive vasodilatation or vasoconstriction exists in the vessels of the forearm or leg.

On the basis of the results obtained with a period of exercise, it appears either that the compensatory circulatory mechanisms elicited by such a stimulus are not as effective as normal, that the work is performed with less efficiency, or possibly that both mechanisms are operating in this condition.

AUTHORS.

Cotton, T. F.: *Some Aspects of Carditis*. Brit. M. J. 2: 473, 1942.

Observations are made on the prognosis in carditis, based on the after-histories of two hundred boys, average age 11 years.

Rather more than one-half of the children with carditis are alive and slightly more than one-third are dead ten years after from four and one-half to six months' treatment in a special convalescent home. The large number of untraced cases prevents the author from concluding that the prognosis is more favorable when the stay in a convalescent home is increased from four and one-half to six months.

Rather less than half of those who die within ten years live longer than five years after treatment in a special convalescent home.

The death rate in children with mitral stenosis and aortic regurgitation is much higher than in those with mitral systolic murmurs, over a 10-year period.

Children with moderate or considerable enlargement of the heart are less likely to live ten years than those with slight or no enlargement.

AUTHOR.

Strassmann, G., and Goldstein, P.: *Syphilis of the Aorta and Coronary Arteries*. Arch. Path. 34: 745, 1942.

Sudden death caused by syphilitic aortitis associated with stenosis or occlusion of the orifice of one or both coronary arteries is fairly common. Syphilitic aortitis is often associated with arteriosclerosis of the coronary arteries. Seventeen of twenty-eight cases of sudden death caused by syphilitic aortitis with stenosis of the mouths of the coronary arteries investigated by the Office of the Chief Medical Examiner of the City of New York in Manhattan during the years 1940 and 1941 showed moderate or advanced coronary arteriosclerosis. A combination of syphilitic aortitis with syphilis of the coronary arteries distal to their orifices is, however, rare.

The case which the authors report showed a combination of syphilitic aortitis and syphilitic coronary arteritis. The aortitis produced stenosis of the orifices of both coronary arteries and the arteritis resulted in marked narrowing of the lumen of the main branches of both vessels. In combination, these two processes impaired the blood supply of the myocardium and were undoubtedly responsible for the sudden death.

AUTHORS.

Hamilton-Paterson, J. L., and Castleden, L. I. M.: *Intracardiac Tumors*. Brit. Heart J. 4: 103, 1942.

Three cases of intracardiac tumor are described, a sarcoma, a "pseudomyxoma," and an aneurysm, which produced signs and symptoms attributable to Ayerza's syndrome, mitral stenosis, and pulmonary stenosis respectively.

The origin of pseudomyxomata of the heart is discussed. It is suggested that they are not primarily neoplastic but are pedunculated thrombi as all their histological features may be reproduced in organizing blood clots.

A classification of heart tumors is suggested: Benign tumors resulting from organization of blood clot—pseudomyxomata; malignant tumors arising from any of the mesenchymal elements of the heart wall, the true sarcomata; and benign congenital tumors arising from developing myocardial elements, the congenital rhabdomyomata (dysontogenetic rhabdomyoma, hamartoma).

AUTHORS.

Solomon, C., Roberts, J. E., and Lisa, J. R.: The Heart in Uremia. *Am. J. Path.* 18: 729, 1942.

The pathological findings in fifty hearts of patients dying in uremia are reported. No lesion was found which could be considered characteristic of the uremic state. In seven of eight cases with acute necrotizing arteriolitis of the kidneys, an unusual endothelial hyperplasia of the cardiac arterioles was present. In no other type of renal pathology was there any correlation with the cardiac changes. There was a definite relation between the presence of acute lesions of the myocardial fibers and the occurrence of clinical signs of cardiac dysfunction.

WILLIAMS.

Roth, G. M., and Sheard, C.: The Effect of Peripheral Vasodilatation on Vasoconstriction: Determinations Made on the Basis of Blood Pressure of Normal Subjects. *Am. J. Physiol.* 137: 695, 1942.

In these twelve normal subjects, irrespective of the basal metabolic rate and irrespective of the existing generalized peripheral vasodilatation, the response to the vasoconstricting agent was not altered significantly.

AUTHORS.

Eichna, L. W., and Wilkins, R. W.: Capillary Blood Pressure in Man. Direct Measurements in the Digits During Induced Vasoconstriction. *J. Clin. Investigation* 21: 697, 1942.

In the normal-sized digital capillaries of healthy subjects and of hypertensive patients, neurogenic vasoconstrictor stimuli brought about decreases in capillary blood pressure of from 5 per cent to 33 per cent.

Reflex vasodilatation in the digit, even when combined with local vasodilatation produced by histamine, failed to prevent the fall in capillary blood pressure which occurred in response to neurogenic vasoconstrictor stimuli.

The percentage variation in digital capillary blood pressure was considerably smaller than the percentage variation in digital blood flow which has been reported to occur during similarly induced vasoconstrictions.

In the abnormally large digital capillaries of patients with Raynaud's disease and scleroderma, neurogenic vasoconstrictions, and vasoconstrictions induced by the intravenous injection of epinephrin, were usually accompanied by decreases in capillary blood pressure.

After interruption of the sympathetic nervous pathways to the digits of patients with Raynaud's disease and scleroderma, neurogenic vasoconstrictor stimuli failed to induce in the sympathectomized digits either vasoconstriction or fall in capillary blood pressure. On the other hand, intravenously injected epinephrine continued to cause both vasoconstriction and fall in capillary blood pressures.

These observations have been interpreted as indicating (a) that although strong physiologic vasoconstriction mediated through sympathetic nervous pathways may be accompanied by a fall in digital capillary blood pressure, the fall is relatively slight; and (b) that the digital capillary blood pressure may remain at a relatively constant level during wide fluctuations in digital blood flow.

AUTHORS.

Schafer, P. W.: Body Fluid Changes in Neurogenic Hypertension and Total Paravertebral Sympathectomy. *Proc. Soc. Exper. Biol. & Med.* 49: 327, 1942.

Changes in blood volume, plasma volume, hematocrit and red blood cell count have been studied in hypertensive dogs subjected to total paravertebral sympathectomy and in sympathectomized dogs subjected to the procedure used for production of hypertension. It was found that dogs subjected to modulator nerve

section developed marked hypertension and a markedly increased total blood volume apparently due to an increase in the cellular fraction of the blood. When these dogs were subjected to total paravertebral sympathectomy they regained approximately a normal total blood volume and their hypertension was markedly reduced; these changes were apparently due to a decrease in cells alone as the plasma volume remained unchanged. Normal dogs subjected to total paravertebral sympathectomy developed a slight hypotension and a slightly increased total blood volume due to an increase in the plasma fraction of the blood. When these sympathectomized dogs were subjected to modulator nerve section they developed a moderate hypertension not associated with any significant change in total blood volume, either in its cellular or plasma fraction.

WILLIAMS.

Kempf, G. F., and Page, I. H.: Production of Experimental Hypertension and the Indirect Determination of Systolic Arterial Pressure in Rats. *J. Lab. & Clin. Med.* 27: 1192, 1942.

Silk perinephritis and constriction of the renal artery by a silk thread both elicit arterial hypertension in rats of a degree sufficient for assay of renal antipressor extracts. The preparation of hypertensive rats by these methods is described.

The method of Williams, Harrison, and Grollman for measurement of systolic blood pressure has been modified to increase its effectiveness.

AUTHORS.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Study of the Influence of the Character of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects. *J. Clin. Investigation* 21: 651, 1942.

Objective evidence supports the belief that the conditions under which physiological studies are carried out must be suitably arranged, not only to assure uniform temperature, humidity, and state of digestion, but also less tangible factors such as the patient's mental comfort and the degree of his relaxation. This was demonstrated by converting a "laboratory" into a conventional bedroom and by observing how the frequency of reaction on the part of peripheral blood vessels increased when sensory stimuli were applied at distant parts of the body. This observation was made not only in the case of groups of hypertensive and senile subjects but also in individual subjects studied under both types of environment. Conversely, in tense individuals, to be unable to relax in the atmosphere of a "laboratory" is evidence of the possible presence of an abnormal process.

AUTHORS.

Burch, G. E., Cohn, A. E., and Neumann, C.: Reactivity of Intact Blood Vessels of the Fingers and Toes to Sensory Stimuli in Normal Resting Adults, in Patients With Hypertension, and in Senile Subjects. *J. Clin. Investigation* 21: 655, 1942.

The mean reaction times in the tips of the fingers in normal (3.12) and in senile persons (3.86) differ from those in hypertensive patients (2.94), being more rapid in the hypertensive and slowest in the senile persons. In the tips of the toes, the general arrangement is the same, being fastest in hypertensive patients (3.24) and slowest in the senile (4.25). In the toes, the delay (beyond the fingers) is of the same order of magnitude in each of the three groups. This can be accounted for on the basis of the time required for the efferent impulses to traverse the additional length of post-ganglionic sympathetic fibers in order to reach the toes. The stimuli used were diffuse light, heat, cold, pin-prick, sudden loud noise (pistol-shot), and

electric shock. There was no significant difference in the normal group among the stimuli used in the reaction time or in any part of the total vascular response, such as time for the vasoconstriction to reach a maximum, degree of change in the volume of the pulse wave, time for recovery, and suddenness of response. It was not possible to group persons on the basis of their reactions to the stimuli.

The stimuli, light and bell, which were applied while subjects were alone were more satisfactory than those which, when applied, necessitated the presence of an observer. Psychological factors, often apparently very mild, influenced the responses significantly, which indicated the extreme importance of recognizing them during peripheral vascular studies on conscious human beings.

No correlation was found, provided a reaction to the stimulus occurred, between the reaction time and the state of the vascular bed of the part. The reaction time was essentially not affected by the fact that the vascular bed was already in a contracted or dilated state or was constricting or dilating when the stimulus was applied. This was not the case concerning the degree of change in volume of the vascular bed during the response. The more constricted the vascular bed at the time of stimulation, the less change in volume.

In general, the data strongly suggest that reaction time was more rapid, the vascular response occurred more suddenly and to a greater degree and was over more rapidly, in hypertensive than in normal subjects.

In the senile subjects, the reaction time was less rapid than normal and the vascular response occurred more slowly, to a less degree, and the recovery was much slower.

The reason for these differences is unknown. These differences can be owing to changes in the vessels themselves or in factors outside the vessels such as the nervous system or in chemical states which influence the vessels.

AUTHORS.

Di Palma, J. R., and Foster, F. I.: Sensitivity of the Smallest Cutaneous Blood Vessels: Quantitative Responses to Graded Mechanical Stimulation and to Local Ischemia in Arterial Hypertension, Arteriosclerosis, and Certain Allied Disorders. J. Clin. Investigation 21: 675, 1942.

The responses to graded mechanical stimulation, and to local ischemia of the smallest blood vessels of the skin of the ventral surface of the forearm, were quantitated in fifty patients with arterial hypertension twenty-five patients with arterial hypertension associated with arteriosclerosis, and twenty-three patients with arteriosclerosis. Also included in this study were eleven cases of malignant hypertension, and thirteen cases of hypertension associated with various types of nerve lesions, which influenced their capillary sensitivity. These results were compared to similar studies of a suitable control group of thirty-two subjects. The implications of the abnormal responses obtained were discussed. The following conclusions were reached.

In the group with arterial hypertension, it was demonstrated that the responses of the small dermal vessels, as quantitated in this study, are in no way significantly different from those of a comparable normal group.

No relationship was found between the severity of the hypertensive process, excluding the malignant phase, and the functional responses of the small cutaneous vessels. Many cases of very severe hypertension with diastolic blood pressures of over 130 mm. Hg. were studied, and showed normal capillary responses.

The conclusions for the purely hypertensive group apply as well to those patients with hypertension associated with arteriosclerosis, and with uncomplicated arteriosclerosis.

Of eleven patients with the malignant syndrome of hypertension, ten had small blood vessel responses which indicated greatly decreased sensitivity. This was especially evidenced, in five of these patients, by a complete inability of the small dermal vessels to respond by reactive hyperemia to local ischemia.

Thirteen patients with hypertension complicated by a nerve lesion, ranging from a cerebral vascular accident to Parkinson's disease, were found to have small cutaneous vessels as much as eighteen times more sensitive than the normal or hypertensive groups. Very irritable, small, dermal blood vessels may therefore exist even in the presence of arterial hypertension.

The above conclusions suggest that the humoral agent now believed responsible for arterial hypertension does not exert its influence upon the smallest blood vessels in the benign stages of the disease but may do so in the later malignant phase. If this is confirmed, the quantitative responses of the small dermal vessels might serve as a criterion of the extent of the vascular lesions in advancing hypertensive disease.

AUTHORS.

Katz, L. N., Shleser, I. H., Asher, R., and Perlow, S.: Prevention of Experimental Shock Following Venous Occlusion in the Dog by the Application of a Rigid Cast. *Am. J. Physiol.* 137: 589, 1942.

In a series of thirteen dogs the application of a plaster cast for thirty-six hours to the lower extremities led to the survival of eleven animals following venous occlusion of the limb. Only one dog died in shock. This contrasts with the development of shock in thirteen out of fifteen dogs following this operation when no cast is applied, death occurring in three and one-half to twenty-one hours.

These results indicate that the cast by preventing the local accumulation of plasma fluid avoided the shock syndrome.

The local fluid accumulation which occurred following the removal of the cast developed at a slower rate than in the control series. The absence of untoward results in the period following removal of the cast suggests that for the shock syndrome to become established the loss of plasma fluids must occur at a rapid rate, a rate faster than compensating mechanisms can cope with.

This casting procedure appears to be applicable clinically for use in both civilian and military crush injuries.

AUTHORS.

Schecter, A. E., Cullen, M. L., and Freeman, N. E.: The Production of Shock by Trauma After Spinal Cord Transection. *Am. J. Physiol.* 137: 710, 1942.

The spinal cord was transected between the first and second thoracic vertebrae in eight dogs. The animals were studied two or more days after recovery from this operation. The muscles of one hind leg were traumatized by 1,000 blows with a rubber hammer, and the bones of the extremity were fractured with a heavy metal bar. Blood loss into the area of injury was restricted by binding the extremity. The adequacy of circulation was determined by measurements of blood pressure, peripheral blood flow, cardiac output and oxygen content of mixed venous blood. Pathological changes characteristic of shock were found at post mortem. A reduction of blood volume and hemoconcentration occurred after trauma in the presence of a well-maintained circulation and in the absence of excessive blood loss into the injured extremities. These findings suggest the action of some factor capable of causing a reduction in blood volume not primarily due to excessive loss or to reduced circulation.

ROTH.

Bancker, E. A., Jr.: Coronary Thrombosis: Report of a Study of Fifty-Five Cases. *J. M. A. Georgia* 31: 156, 1942.

In the fifty-five cases reported, posterior thrombosis outnumbered anterior thrombosis by one. The mortality rate was 38 per cent.

AUTHOR.

Waldman, S.: A Method for Rapid, Repeated, Approximate Determinations of the Transverse Diameter of the Heart. *J. Lab. & Clin. Med.* 28: 201, 1942.

A simple method of immediate approximate measurement of the transverse diameter of the heart is described, obviating to a certain extent the use of orthodiagrams and teleoroentgenograms. Repeated studies in the same patient give excellent comparative results, and changes in the size of the heart are easily observed and recorded. Film is conserved, and time and expense are reduced to a minimum.

AUTHOR.

Leach, J. E., and Sugiura, K.: Late Effect of High Voltage Roentgen Rays on the Heart of Adult Rats. *Am. J. Roentgenol.* 48: 81, 1942.

Doses of from 750 to 7,500 roentgens of 200 K.V. roentgen rays were given over the heart of adult rats. The animals were sacrificed at intervals of from four to fifteen months later and the hearts examined grossly and microscopically. These doses produced no demonstrable effects on the hearts. The fluid flow theory of Failla was applied to explain the relative resistance of the myocardium to roentgen irradiation.

WILLIAMS.

Wheeler, Sir W. I. de C.: Ligature of Innominate Artery for Right Subclavian Aneurysm: End-Result. *Brit. M. J.* 2: 422, 1942.

Ligature of the innominate artery is not a difficult operation provided the exposure is adequate. Exploration, and the clearing of the deep surface of the manubrium sterni, are greatly facilitated by turning down the middle portion of the clavicle. In most cases this should be the first major step in the operation.

If ligature of the innominate is seen to be necessary a portion of the sternum should be divided and retracted upwards with the inner end of the clavicle. This can be accomplished without division of the first costal cartilage.

AUTHOR.

Westcott, F. H.: Social Aspect of Heart Disease in Industry. *New York State J. Med.* 42: 955, 1942.

Illness accounts for 75 per cent of lost time in a large commercial organization, as compared to 25 per cent lost by reason of injuries. About 8 per cent of total time loss is due to cardiovascular disease.

The amount of time lost for cardiac disease is greatest in the case of unexamined and unselected employees and least in the case of those employed as group A risks.

The percentage of cardiacs losing time is smallest in the D group—those not covered by disability—and highest among the older employees entitled to all disability benefits.

Chronic myocarditis with decompensation and arteriosclerotic cardiovascular disease constitute at least 50 per cent of all cardiac disability.

By selective physical employment and a graded sick benefit plan, those employees liable to lose time because of heart disease other than from acute accidents, can be segregated and given gainful work of a type in which further damage to a diseased heart is avoided. Such a plan of employment eliminates the danger of setting up a social and economic inequality in the case of certain applicants.

AUTHOR.

Bondy, P. K., and Altschule, M. D.: The Action of Furfmethide (Furfuryl-Trimethyl-Ammonium Iodid) on the Cardiovascular System in Man. *Am. J. M. Sc.* 204: 334, 1942.

The reactions of 29 patients to the parasympathomimetic drug Furfmethide (furfuryl-trimethyl-ammonium iodid) in parenteral doses of 3 to 20 mg., and in oral doses of 10 to 35 mg., were studied. Particular attention was paid to its effects on the cardiovascular system. Transient falls of systolic and diastolic blood pressures, tachycardia and rises of venous pressure occurred in patients receiving the drug parenterally. No such reactions occurred in patients receiving the drug orally. The side reactions include flush, sweating and urgency of urination. In the doses recommended for the treatment of atonic bladders (i.e., 3 to 5 mg. subcutaneously or 10 to 25 mg. orally) these reactions were not so marked as to make the patient uncomfortable.

The drug may safely be repeated after an hour when given subcutaneously, or after 4 hours when given orally.

Large doses of Furfmethide should not be given parenterally to old patients or patients with known heart disease, as the tachycardia and fall in blood pressure may give rise to myocardial infarction. Very small doses should be used first in such patients, gradually increasing the dose after it has been shown that the smallest doses are without effect. The use of Furfmethide by the oral route appears to be preferable in patients with heart disease.

Patients receiving Furfmethide parenterally should be kept covered and in bed until the flush reaction has worn off, in order to guard against great losses of body heat during the sweating and vasomotor reactions.

AUTHORS.

Moia, B., and Quesada, R.: The Treatment of Arterial Hypertension by Thyocyanate. *Rev. argent. de cardiol.* 9: 41, 1942.

Thirty patients with essential hypertension, with blood pressures over 200 mm. Hg systolic and 120 mm. Hg diastolic were used in this study. None of them were in the malignant phase or had congestive cardiac failure. After more than 4 years of treatment with usual therapeutic means, they received during 10 months, as exclusive treatment, potassium thyocyanate 0.30-0.60 gr. daily. The hematic concentration of the drug was explored weekly by the micro-method of Griffith and Lindauer, slightly modified.

The results obtained were good (group I) and 6 cases (20 per cent) with a decrease in blood pressure of 70-80 mm. Hg systolic and 20-25 diastolic; fairly good (group II) in 13 cases (43.3 per cent) with a decrease of 30-40 mm. Hg and 10-15 mm. Hg systolic and diastolic pressure respectively. Greater doses did not alter the results in this group even when levels higher than 10 mg. of potassium cyanate per cent were reached in the blood. In the other 19 patients (36.7 per cent) the results were bad (group III).

No relation was found between the condition of the eyegrounds and the results obtained. But it was found that patients in which the blood pressure was unstable responded better to treatment by thyocyanate: the results in these patients were more favorable and persistent.

All the patients of group I and some of group II were relieved of subjective symptoms, not so those of group III. Generally speaking the subjective amelioration obtained by autohemotherapy was more accentuated and lasting than with thyocyanate therapy, and moreover did not cause any of the disturbance which appear specially during the first days of treatment in the majority of the patients which receive thyocyanate. Only two patients had intolerance phenomena: benign erritrodermia which rapidly disappeared on withdrawal of the drug.

It is concluded that the administration of thiocyanate should be continued only when results comparable to those of group I are obtained or else, even if no reduction in blood pressure is obtained, when the amelioration of subjective symptoms is greater than that which can be attained by other therapeutic measures.

AUTHORS.

Wood, E. H., and Moe, G. K.: Blood Electrolyte Changes in the Heart-Lung Preparation With Special Reference to the Effects of Cardiac Glycosides. *Am. J. Physiol.* 137: 6, 1942.

The effects of digitalis glycosides on blood electrolyte levels have been studied in 75 heart-lung preparations and in a number of control experiments. In some of these experiments whole blood potassium, glucose, cell volume, and serum sodium, calcium, and chloride analyses have also been carried out. These analyses and calculations based upon these analyses lead to the following conclusions: (1) In an untreated control heart-lung preparation a variable degree of hemo-concentration, a tendency for a slow increase in serum potassium, and a progressive fall of blood glucose occur. Constant changes in serum sodium, calcium, and chloride were not found. (2) Suitable doses of digitalis cause concomitant increases in external mechanical efficiency and blood and serum potassium along with a questionable decrease in serum potassium along with a questionable decrease in serum sodium. Significant differences from the untreated preparations were not demonstrated in the other blood components studied. (3) Therapeutic doses of digitalis glycosides produce relatively small but apparently significant increases in serum potassium. (4) A positive correlation was demonstrated between the total dose of a digitalis glycoside and the rate of serum potassium increase both during the efficiency increase period and for the duration of the drug's action. (5) The increased external efficiency and increased rate of potassium liberation which occur after suitable doses of digitalis are concomitant phenomena but a simple relationship between these two actions of digitalis on the heart-lung preparation is not evident. (6) Little if any correlation was found between the time of onset of digitalis irregularities and the rate of serum potassium increase or the potassium concentration of circulating serum. (7) The relative potassium mobilizing powers of the glycosides studied correspond somewhat more closely to their relative therapeutic activities than to their relative toxicities for the heart-lung preparation. (8) An increase in blood and serum potassium results from the action of suitable doses of digitalis glycosides in both the completely isolated heart and the completely isolated lung preparations. (9) The increased blood potassium resulting from digitalis action on the heart-lung preparation originates from both the heart and lung tissue.

AUTHORS.

Katz, L. N., Killian, S. T., Asher, R., and Perlow, S.: The Prophylactic Action of Desoxycorticosterone in Shock Due to Massive Venous Thrombosis. *Am. J. Physiol.* 137: 79, 1942.

Experimental massive venous occlusion of a leg leads to a fall in blood pressure, a rise in hematocrit and an increase in the size of the leg amounting to 2.3 to 6.9 per cent of the body weight. This results in death in 3½ to from 12 to 21 hours. Only an occasional animal survives (2 out of 15 in our series).

The administration of desoxycorticosterone acetate (DCA) over a period of 24 hours previous to, and during the first 24 hours after the onset of the venous occlusion prevents the development of the state of shock and the animals survive (8 out of 11 in our series) despite a loss of fluid comparable to that in the control series.

When the DCA is not given sufficiently early before the onset of venous occlusion, the picture of shock and the mortality are similar to those of the untreated animals (death occurred in 8 out of 9). However, the average time of death is delayed somewhat and the loss of fluid is greater.

Evidence is given to show that DCA decreases the rate of fluid loss due presumably to some action on the oncotic pressure of the blood.

The action of DCA in preventing shock and the development of an irreversible state is due to some other mechanism in addition to its action on fluid loss from the blood. The nature of this action was not revealed by these studies.

AUTHORS.

Follis, R. H., Jr.: Myocardial Necroses in Rats on a Potassium Low Diet Prevented by Thiamine Deficiency. Bull. Johns Hopkins Hosp. 71: 235, 1942.

The production of thiamine deficiency together with potassium deficiency in rats exerted a protective effect in these animals in that no myocardial necroses such as are seen in potassium deficiency developed. Possible explanations for this "protective" effect are considered.

Unlike observations in certain other species no cardiac changes were observed in rats on a thiamine deficient diet.

Changes in the kidneys characteristic of potassium deficiency did develop in all animals whether potassium alone or potassium together with thiamine was lacking.

In all but two of the sixteen potassium-thiamine deficient animals necroses of the voluntary muscle fibers were observed.

AUTHOR.

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Original Communications

PULMONARY EMBOLISM WITH AND WITHOUT ACUTE COR PULMONALE, WITH ESPECIAL REFERENCE TO THE ELECTROCARDIOGRAM

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PAUL D. WHITE, M.D.
BOSTON, MASS.

PULMONARY embolism, always a common condition, has only in recent years begun to attract as much attention on the part of internists as it deserves. Surgeons and obstetricians have been more or less aware of thrombophlebitis and pulmonary embolism as complications of operations and childbirth for generations, but physicians at large have not been cognizant of the large role that peripheral (especially in the leg) thrombophlebitis and pulmonary embolism play in complicating or simulating either acute or chronic illness of a medical nature. Now that a healthy change in viewpoint is beginning, it is imperative that there be a clear recognition of the most important symptoms and signs of these conditions. There tend to be, for example, in thrombophlebitis a slight degree of fever and leucocytosis and an increase in the sedimentation rate, even though there may be very little objective evidence on physical examination prior to the occurrence of pulmonary embolism. And in the case of pulmonary embolism itself, there are many suggestive symptoms and signs, including sudden dyspnea or oppression in the chest, tachycardia otherwise unexplained, fever, leucocytosis, râles in the lungs, even at both bases in the absence of congestive failure, and, relatively infrequently, the classical signs of extensive pulmonary consolidation, with or without pleuritis and hemoptysis.

One of the methods of study which has given positive results in some cases of pulmonary embolism is electrocardiography, but confusion exists in the literature as to its exact place in the diagnosis of the condition. It is our aim to help to clarify the situation by pointing out, first, that in the minority of cases the changes may be pathognomonic, second, that

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nondiagnostic changes may occur, as in the case of myocardial ischemia, particularly in the presence of important pre-existing coronary heart disease, and, third, that in many cases of pulmonary embolism one should not expect to find any electrocardiographic changes at all.

The literature contains several contributions on pulmonary embolism in which most of the emphasis has been placed on the electrocardiographic abnormalities. Not all the observers agree that constant variations do occur. Confusion has arisen because of the failure to make the distinction between those with, and those without, acute cor pulmonale. Barnes¹ pointed out that patients with the greatest circulatory embarrassment, together with features of shock, were the most likely to have the typical electrocardiographic changes. Love, Brugler, and Winslow² reported twelve cases of pulmonary embolism, of which seven showed all or most of the characteristic changes. Stewart, Kirk, and Smith³ studied twelve cases of pulmonary embolism, in five of which the diagnosis was confirmed by post-mortem examination. These cases were selected from a larger group in which there were complicating factors which, by themselves, could modify the electrocardiogram. Their observations were essentially the same as those originally noted by McGinn and White⁴ and those to be reported in this paper. Scherf and Schönbrunner⁵ reported eight cases (no autopsies), in only one of which were there typical electrocardiographic changes. Sokolow, Katz, and Muscovitz⁶ reported fifty unselected cases of pulmonary embolism, with twenty-seven autopsies, and reviewed the electrocardiographic observations. Five patients showed the changes described as occurring in acute cor pulmonale; of the remainder, nineteen had heart disease prior to the occurrence of the embolism, twenty-seven had electrocardiographic changes which, they said, may have antedated the embolism, and nine showed some of the characteristics of recent myocardial infarction in their electrocardiograms. They stressed the importance of putting the chest electrode over the right ventricle in order to obtain the typical inversion of the precordial T wave, which they attributed, as have we, to strain on that chamber. Horn, Dack, and Friedberg⁷ studied forty-two cases of pulmonary embolism and found evidence of recent structural damage in the myocardium in eight cases. In these the embolism was recurrent, and several days had elapsed before death, allowing time, they considered, for such changes to occur. These authors believe that the myocardial changes were the result of ischemia, and that they accounted for the electrocardiographic variations. They suggest that diminished blood flow through the right coronary artery, caused by increased tension in the right ventricle, may explain the resemblance of the electrocardiographic changes in cases of pulmonary embolism to those in myocardial infarction of the posterior wall. Some of the hearts in which these changes were reported showed an increase in weight, muscle hypertrophy, and disease of the coronary arteries. Wood,⁸ in presenting ten unselected cases of pulmonary embolism, pointed out the result of

different chest electrode positions on the precordial lead. He found that the T-wave inversion was (1) maximal and for the longest duration with the electrode in the right "pectoral" position, (2) usually present, but for a shorter time, when the electrode was in the left "pectoral" position,* and (3) rarely present, and for the shortest time, with the electrode over the apex of the heart. He placed the indifferent electrode on the right arm (the modern IV-R, or CR). Love, Brugler, and Winslow² produced pulmonary embolism in dogs experimentally, using clotted autogenous blood. They concluded that dilatation of the right ventricle was the significant factor in altering the electrocardiogram, and, furthermore, that myocardial anoxemia and reflexes through the vagus or sympathetic nerves played no important roles.

ACUTE COR PULMONALE IN PULMONARY EMBOLISM

The acute cor pulmonale was described by McGinn and White⁴ as the result of sudden distention of the right ventricle and auricle which followed obstruction to the pulmonary circulation by an embolus. They observed that certain consistent variations from the normal appeared in the electrocardiograms of a number of patients with this condition.

Ten additional cases of acute cor pulmonale are now presented, with their electrocardiograms, to analyze further such changes as were noted in the original article. The cases were selected so that complicating heart disease and other factors which of themselves may modify the electrocardiogram were excluded. Five patients died, of which number three were examined post mortem; and five survived.

For comparison, the data on ninety-two other cases of pulmonary embolism, in forty-two of which the diagnosis was substantiated at autopsy, have been reviewed with particular reference to the electrocardiographic changes, and will be discussed later.

The typical variations which occurred in the electrocardiograms of the ten patients with acute cor pulmonale were (1) the presence of, or a tendency towards, right axis deviation, with a prominent S wave in Lead I (the S-T segment may be slightly depressed in this lead), (2) a depressed S-T take-off in Lead II, followed by a rising S-T segment and a low, upright, or diphasic T wave, (3) a moderately deep Q wave, slight convexity of the S-T segment, and an inverted T wave in Lead III,[†] and (4) a diphasic, or, more often, an inverted T wave in Lead IV. (Lead IV-F, as recommended by the American Heart Association, was used throughout this study.)

Although the signs and symptoms in cases of nonfatal pulmonary embolism with acute cor pulmonale are becoming better known, the condition is of sufficient importance to demand a brief review of them. The

*The "pectoral" position is halfway between the midsternal line and the mid-clavicular line; the exploring chest electrode was connected with the left leg wire.

[†]Slight elevation of the S-T take-off in Lead III was also observed in a few cases of acute cor pulmonale.

outstanding clinical feature is the sudden onset of dyspnea or oppressive anterior thoracic pain, with or without a feeling of faintness, accompanied by rapid, shallow respirations and tachycardia. The patient may show evidence of increased venous pressure, with cyanosis, distended neck veins, and an increased pulmonic second sound. If shock and collapse predominate, the patient becomes pale, cold, and clammy, shows a marked fall in blood pressure, and has a fast, thready pulse. Many patients at first present the signs of increased venous pressure, which are soon followed by a state of shock. They may closely simulate patients with acute coronary occlusion when seen in this condition. Later, with the pleuritis which usually accompanies a pulmonary infarct, there may be pain on breathing, in one side of the chest or the other, or in the back, or even in one shoulder if the diaphragmatic portion of the pleura is involved.

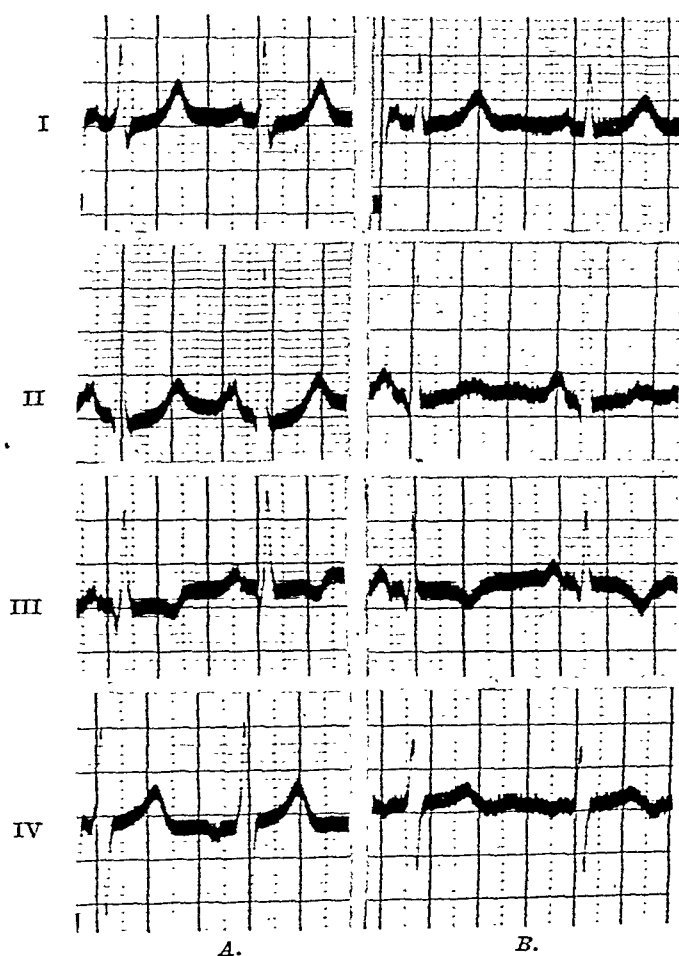


Fig. 1.—Case 1, M. D. P. A. February 23, 1940, three hours after first attack. B. February 26, 1940.

TEN NEW CASES OF ACUTE COR PULMONALE

CASE 1.—M. D. P., a 70-year-old woman, was admitted to the hospital February 10, 1940, with a dislocated left shoulder joint, complicated by a fracture of the great tuberosity of the humerus—the result of a fall the previous day. Reduction was carried out successfully under gas and oxygen anesthesia on February 11. Con-

valescence was uneventful until February 23, when the patient complained of a fainting spell, with substernal discomfort of sudden onset. She became very cyanotic and had difficulty in breathing. The pulse rate was 100, and the temperature was normal. Shortly after the onset, blood pressure was 90/50; within a few hours it rose to 110/70.

An electrocardiogram which was taken about three hours after the attack (Fig. 1-A) showed normal rhythm, a rate of 105, a short, but distinct, S wave in Lead I, and depression of the S-T segments in Lead I and Lead II. In Lead III a small Q wave was present, and the T wave was deeply inverted. The chest lead was normal. She improved rapidly with the aid of oxygen. A roentgenogram of the chest on February 26 showed haziness at the outer border of the left lung, below the scapula. An electrocardiogram on February 26 (Fig. 1-B) showed normal rhythm and a rate of 85. The S-T segments in Leads I and II had returned almost to the isoelectric line. The S waves in Lead I had practically vanished. A Q wave and a deeply inverted T wave were still present in Lead III. The T wave in Lead IV was low and slightly diphasic. On March 4, the patient suddenly collapsed, became ashen, cold, and clammy, and had a very weak pulse. The blood pressure was unobtainable. Marked air hunger and respiratory embarrassment were obvious, and she died in fifteen minutes.

At autopsy the heart weighed 350 grams; the right ventricular wall measured 4 mm., and the left, 14 mm., in thickness. The myocardium and the valves were normal. The right ventricle was slightly dilated, but the left was normal. Along the lateral portion and base of the left lung there was a wedge-shaped, red-brown infarct, 7 by 4 by 4 cm. A vessel proximal to it was occluded by a gray-red embolus. No other infarcts were seen, but ante-mortem emboli were scattered through the right lower lobe. The main pulmonary artery and its branches were occluded completely by a long, granular, coiled embolus. In the left popliteal vein, a red, granular thrombus similar to that in the pulmonary artery and its branches was present, and was partially adherent to the vessel wall. The left leg was slightly larger than the right.

CASE 2.—W. R., a housewife, 40 years old and moderately obese, had injection treatment of varicose veins in both legs during 1937. In July, 1939, phlebitis occurred in the right leg, with thrombosis of the long saphenous vein, which became palpable up into the groin. A few days later she complained of a "chest cold," with right-sided neuralgia that was thought to be the result of sitting in a draft. On August 16, 1939, she experienced acute precordial pain which radiated to her left shoulder and was accompanied by rapid, shallow respirations. After this attack she found that it was extremely painful to breathe deeply, or to move around or roll over in bed. On August 17, physical examination showed that she was well nourished and moderately ill. There was a slight malar flush and her cervical veins were distended. The left border of cardiac dullness was 9 cm. from the midsternal line and 1 cm. outside the midclavicular line. The heart rate was 135. There were no murmurs. The pulmonic second sound was much accentuated, and louder than the aortic second sound. In the third and fourth left intercostal spaces, 1.5 cm. from the sternal margin, a rough, sticky sound (pleuro-pericardial friction rub?) was heard. The blood pressure was 150/90. The lungs and abdomen were negative on examination. In both legs thrombosed varicose veins were easily recognized.

An electrocardiogram (Fig. 2) taken on August 17 showed sinus tachycardia, a rate of 125, and a tendency toward low voltage of the QRS complexes. In Lead I an S wave was present, and the S-T take-off was depressed. In Lead II there was a gradual ascent of the S-T segment, and the T wave was flat. A prominent Q wave and deeply inverted T wave were present in Lead III. In Lead IV the R wave was small, and the T wave was very low. Early on the morning of August 18, the patient felt suddenly faint, but experienced no pain, and died shortly afterwards.

CASE 3.*—F. B., a 22-year-old single woman, was admitted to the hospital April 14, 1941. She had complained of intermittent pain in the right lower quadrant for two years. Physical examination was recorded as negative. An exploratory laparotomy was done on August 15 through a right rectus incision under spinal anesthesia. A mildly injected appendix and a small ovarian cyst were removed, and her immediate postoperative course was reported as satisfactory. She was nervous and restless on the third postoperative day, and had a temperature of 99° to 99.8° F., and a pulse rate of 90 to 100. No local cause was discovered which might explain the symptoms. Her appetite was not good during the subsequent three days. She was catheterized daily for the first five postoperative days, and during

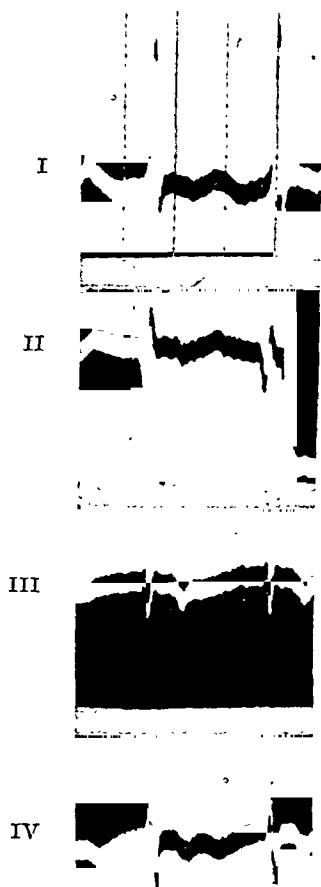


Fig. 2.

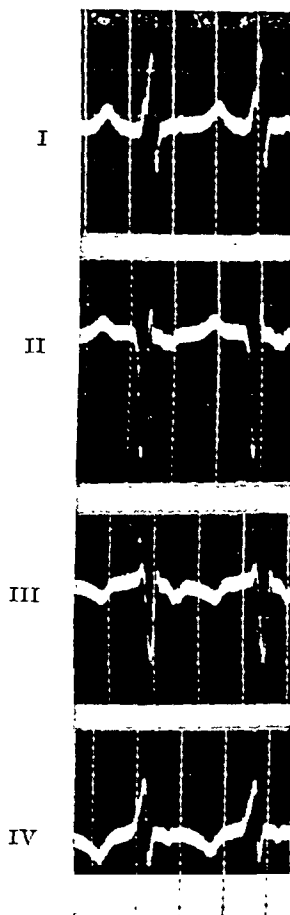


Fig. 3.

Fig. 2.—Case 2, W. R. August 17, 1939, 24 hours after most recent attack.

Fig. 3.—Case 3, F. B. April 24, 1941, 20 hours after first attack, 12 hours after second attack.

this time she developed a profuse vaginal discharge, with considerable pain. She “dangled” on the seventh day, and was out of bed walking in her room on the eighth postoperative day, April 23. That afternoon, while sitting in a chair, the patient complained of a “full” sensation in her chest and of feeling faint. Her face became cyanosed and she rapidly lost consciousness. Her respiration became rapid and stertorous, and no pulse could be felt. Oxygen and stimulants were applied, and the patient soon revived. Her pulse was noted as thready, weak and ir-

*Presented through the courtesy of Dr. Sherman Golden, Beverly, Massachusetts.

regular, with a rate of 120. She was cold and perspiring profusely, and her respirations were rapid, but quiet. During the night she again became cyanotic, pulseless, and complained of pain in her chest. Oxygen, stimulants, and digifolin were administered.

On April 24, twenty hours after the first attack, a consultant reported that she was ashen, apprehensive, and extremely weak. Her skin was cold and clammy. The temperature was 96.8°, the pulse rate, 120, and the respiratory rate, 35. Her blood pressure could not be obtained. The cervical veins were visible, but not engorged. Her heart was not enlarged. A systolic gallop was present over the precordium, and the pulmonary second sound was markedly accentuated and reduplicated. At the base of the left lung, in the posterior axillary region, the breath sounds were harsh, but no râles were heard. The edge of the liver was palpated two fingerbreadths below the right costal margin. There was no peripheral or dependent edema. The urine was normal; the leucocyte count was 18,000, with 81 per cent polymorphonuclears.

An electrocardiogram (Fig. 3), taken April 24, showed sinus tachycardia, a rate of 125, and well-marked right axis deviation. In Lead I there was a deep S wave, with moderate slurring of the upstroke of this wave. The S-T segment was slightly depressed in both Leads I and II. Lead III showed a Q wave and an inverted T wave. The T wave in Lead IV was inverted. The patient died one and one-half hours after the electrocardiogram was taken, and twenty-three hours after the onset of the first attack. Permission for post-mortem examination was not obtained.

CASE 4.—F. W. H., a 73-year-old man, developed a slight feverish cold on September 12, 1940, but was not incapacitated by it. He had an unproductive cough during the next two weeks. There was no history of chills, dyspnea, or chest pain. On October 7 he became feverish without observing any pain, and began to cough more than usual. Physical signs of consolidation of the right lower lobe were found on October 8 by his physician, who administered sulfapyridine. On October 11 he coughed up some bloodtinged sputum. When he was admitted to the hospital on the following day, physical examination showed an elderly man, perspiring and moderately cyanotic, with an emphysematous chest. There were moderate impairment of resonance and distinct bronchial breathing at the base of the right lung; generalized sonorous and sibilant râles were audible, and there were fine râles at the bases of both lungs. His temperature was 100°, his pulse rate, 80, and his blood pressure, 148/68. There had been no previous symptoms of heart disease, and examination of his heart on this occasion showed nothing remarkable. His leucocyte count was 20,000. The sputum was negative for 32 types of pneumococci. A "portable" roentgenogram of his chest, taken October 12, showed density at the right base suggestive of consolidation.

On October 23, an electrocardiogram (Fig. 4-A) showed normal rhythm and a rate of 120. There was a prominent S wave in Lead I, followed by a slight depression of the S-T segment. In Lead III there were a deep Q wave and a slightly inverted T wave. The T wave in Lead IV was upright, but low. A second "portable" roentgenogram, on October 22, showed mottled dullness in both lower lung fields that suggested a "bronchopneumonic process." On October 29, an electrocardiogram (Fig. 4-B) showed normal rhythm and a rate of 95. An S wave was still present in Lead I, but was less prominent than in the previous record. The Q wave was deep, and the T wave was definitely inverted in Lead III. The T wave in Lead IV was definitely lower than in the first tracing.

He improved during his stay in the hospital, and his leucocyte count fell to 11,000 by November 7. The physical signs in his chest diminished considerably. He was to return home on November 12, but complained of pain in his right leg which had troubled him a little in the previous two or three days. Phlebitis in the calf was suspected, for which he was treated conservatively. On November 15 he suffered a

sudden attack marked by extreme dyspnea and intense cyanosis, and died within a few minutes.

At post-mortem examination the heart weighed 425 grams. The right ventricular wall measured 4 mm., and the left, 12 mm., in thickness. The myocardium was firm and of normal color. The coronary arteries showed minimal sclerosis. There was no valvular disease. In the right ventricle a laminated, grayish, coiled thrombus lay twisted around the papillary muscles of the tricuspid valve. The pulmonary artery was distended with a pale, thrombotic mass similar to that which lay in the right ventricle; it penetrated into both main branches and into many of the smaller radicles, almost to the periphery of the lungs on each side, and more markedly in the upper than in the lower lobes. In the upper lobe of the right lung, adjacent to the interlobar septum peripherally, there was a small, brown infarct. In the posterior tibial veins of the right leg, approximately 6 cm. below the knee, there was an adherent clot, 5 to 6 cm. in length, similar in type to those described above.

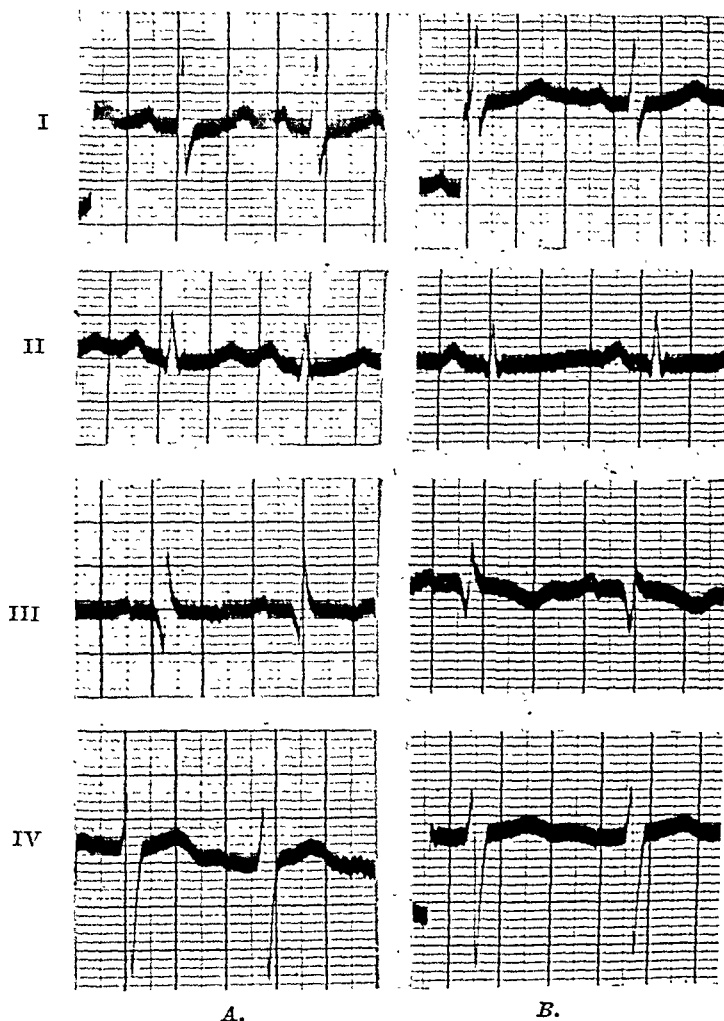


Fig. 4.—Case 4, F. W. H. A. October 23, 1940, several days after pulmonary embolism. B. October 29, 1940.

CASE 5.—D. J. M., aged 26 years, was considered healthy until he complained of weakness while at work on May 18, 1936. He remained in bed at home and had an unproductive cough without chills or fever. After the patient's death, his family physician supplemented this information with the history of chest pain radiating to the back and towards the left side, associated with a sense of dizziness and weak-

ness. When he tried to resume work, on May 25, he noticed weakness and debility, with slight shortness of breath on exertion which had not been present before.

An electrocardiogram (Fig. 5-A), taken May 25, showed sinus tachycardia and a rate of 125. Marked right axis deviation was present. A deep S wave occurred in Lead I, and the S-T segment was depressed in the same lead. The T wave was low in Lead II. The S-T segments were elevated in Lead II and Lead III. In Lead III there were a small Q wave and a deeply inverted T wave. Lead IV was normal. The patient was admitted to the hospital (May 26) because of the suspicious electrocardiographic abnormalities and his unusual history.

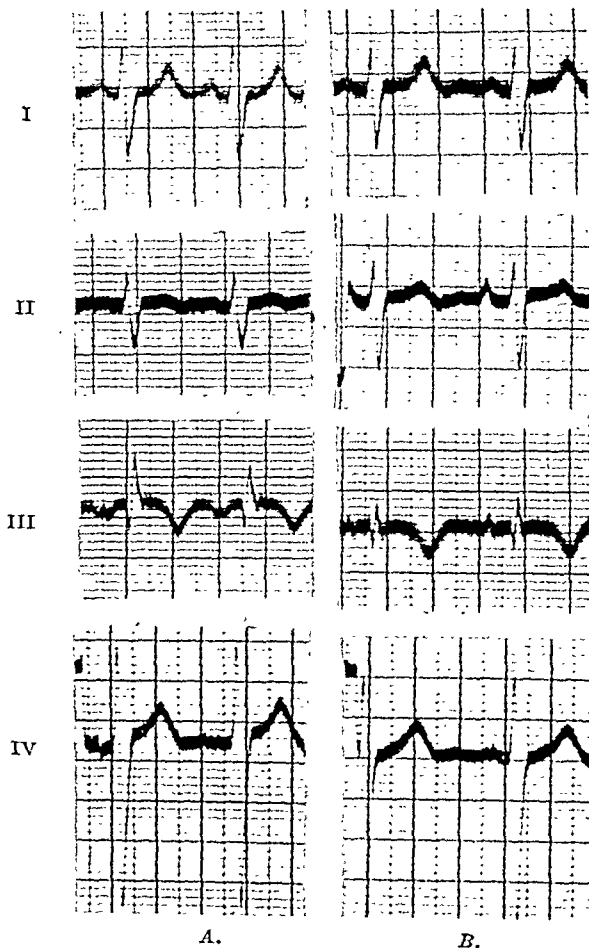


Fig. 5.—Case 5, D. J. M. A. May 25, 1936, several days after pulmonary embolism.
B. May 26, 1936.

On physical examination the left border of his heart was 1 cm. outside the midclavicular line; the apex impulse was forceful and the rate was 120. The first mitral sound was split, but there were no murmurs. The blood pressure varied between 106/80, on admission, and 130/100, two days later. His leucocyte count was 11,800. A second electrocardiogram (Fig. 5-B), taken May 26, showed normal rhythm and a rate of 100, with right axis deviation still prominent. The T wave in Lead II was better defined. The QRS complex in Lead III was variable. He improved with rest in bed during the next three days. On the morning of May 30, after a good night's rest, he sat up in bed to wash, and became cyanotic and unable to breathe or call for aid, and died in a few minutes.

At autopsy his heart weighed 385 grams; the right ventricular wall measured 6 mm., and the left, 15 mm., in thickness. There was marked dilatation of the right ventricle. The valves and coronary arteries were normal. Gross and microscopic examination of the lungs failed to reveal any evidence of infarction or consolidation. In the right pulmonary artery there was a large adherent thrombus where the main vessel divides into the branches to the three lobes. It extended 6 cm. into the main artery of the right lower lobe. Many adherent granular thrombi were found in the other branches of the right pulmonary artery. The arterial branch to the left upper lobe contained an adherent, firm, ante-mortem thrombus; in the left lung the thrombi were more numerous in the smaller arteries than in the larger vessels. In the veins around the prostate and posterior part of the bladder there were numerous adherent thrombi. There was no thrombosis in the leg veins. Microscopically, the right ventricular wall showed much fatty infiltration between some of the muscle fibers near the pericardium.

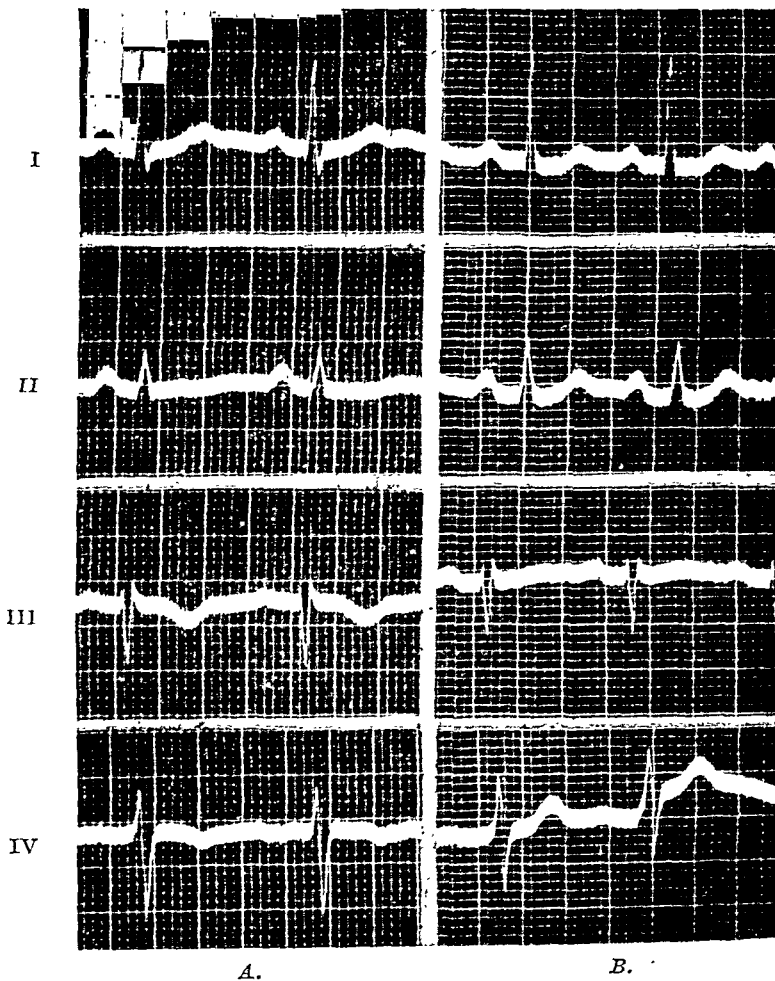


Fig. 6.—Case 6, F. C. A. November 14, 1940, 48 hours after second attack. B. March 2, 1941, follow-up record.

CASE 6.—F. C., an obese housewife, 61 years of age, tripped on a threshold on October 15, 1940, and suffered a fracture and dislocation of her left ankle. Reduction was successfully accomplished on the following day under gas and oxygen anesthesia. The patient improved until November 7, when she experienced an attack of pain beneath the upper part of the sternum, accompanied by quickened respiration. Rapid improvement followed without special treatment. While on a bedpan on November 12, she complained of severe substernal pain and temporarily lost con-

sciousness. A nurse in attendance observed that she was cyanosed and that her respirations were rapid and shallow. Her body became cold and clammy, her pulse was weak, the pulse rate was 130, and her blood pressure fell to 90/60. Later the patient said it was painful to breathe deeply; the pain was felt in the upper part of the left arm and in the left side of the chest. There was no hemoptysis. For an unstated time previous to this attack she had had pain in the calf of her left leg, but it was not of sufficient severity to cause her much concern.

A week later, on November 14, physical examination showed slight cyanosis of the lips. The neck veins were not distended. The left border of cardiac dullness was 8 cm. from the midsternal line, 0.5 cm. inside the midclavicular line. The rhythm was normal, and the rate was 70. A faint aortic systolic murmur was heard. The pulmonic second sound was slightly louder than the aortic second sound. The blood pressure was 106/70. A few moist râles were present along the left costal margin. Edema of the left leg was observed. There was definite tenderness to pressure on the left calf and along the inner aspect of the thigh up to the fossa ovalis. The girth of the limbs just below the tibial tubercles was 16.5 cm. on the left and 14.8 cm. on the right.

An electrocardiogram (Fig. 6-A) on November 14 showed normal rhythm and a rate of 75. In Lead I a small S wave was present, and there was slight depression of the S-T segment. In Lead II the T wave was slightly diphasic. In Lead III a Q wave was prominent and varied somewhat with the respiratory phase, and the T wave was negative. In Lead IV an R wave was present, and the T wave was inverted and shallow.

The patient improved considerably during the winter months. An electrocardiogram (Fig. 6-B) on March 2, 1941, showed normal rhythm and a rate of 85 to 90. The S wave in Lead I had disappeared, and the T wave in Lead II was upright and of normal amplitude. The QRS complex in Lead III was still largely inverted, and the deflections varied with respiration, as recorded in the first tracing. A high position of the diaphragm could best explain these variations in Lead III. In Leads II, III, and IV the T waves had become upright. This record was, therefore, normal.

CASE 7.—L. S., a single woman, aged 27 years, was admitted to the hospital April 30, 1938, with severe right upper quadrant pain radiating around to her back, which was aggravated by deep breathing. The pain began fourteen hours before entry, and was only slightly relieved by morphine. There were no chills, although she felt cold. She was nauseated, but did not vomit. There was no history of jaundice or stool changes. The record did not mention dyspnea, increased respiratory rate, or tachycardia. A month previously the patient had had tonsillitis and a sore throat for four or five days. Eleven days before admission she complained of migratory arthritis, involving the right ankle, right knee, and left wrist.

Physical examination showed a moderately ill woman who was breathing rapidly; her alae nasae were visibly active. There was evidence of localized consolidation at the base of the right lung. Gallop rhythm was present. The heart was not enlarged. The temperature was 104°, the pulse rate, 120, and respiratory rate, 25 to 30. The leucocyte count was 11,000. The diagnoses considered were (1) lobar pneumonia, (2) acute rheumatic fever, with pulmonic involvement, and (3) acute cholecystitis. Roentgenologic examination of the chest on April 30 showed a transverse heart, a high diaphragm on the right side, and haziness in the bases of both lungs. The sputum was negative for pneumococci, and on culture gave a few colonies of alpha and beta hemolytic streptococci. A second roentgenogram, taken May 2, showed definite consolidation of the right lower lobe; this was interpreted as pneumonia.

An electrocardiogram (Fig. 7-A) on May 2 showed normal rhythm, a rate of 105, and a small S wave in Lead I. There was a prominent Q wave in Lead III. The

T wave in Lead IV was inverted. The possibility of pulmonary infarction was suggested because of these changes, together with the history. She improved until May 6, when she suddenly developed a new pain in the right lower, anterior part of the chest and a slight cough without sputum. A roentgenogram on this day showed, in addition to the density in the right lower lobe, as before, other round areas of increased density in the middle and lower portions of the right lung. There were linear scars in the lower lobe of the left lung.

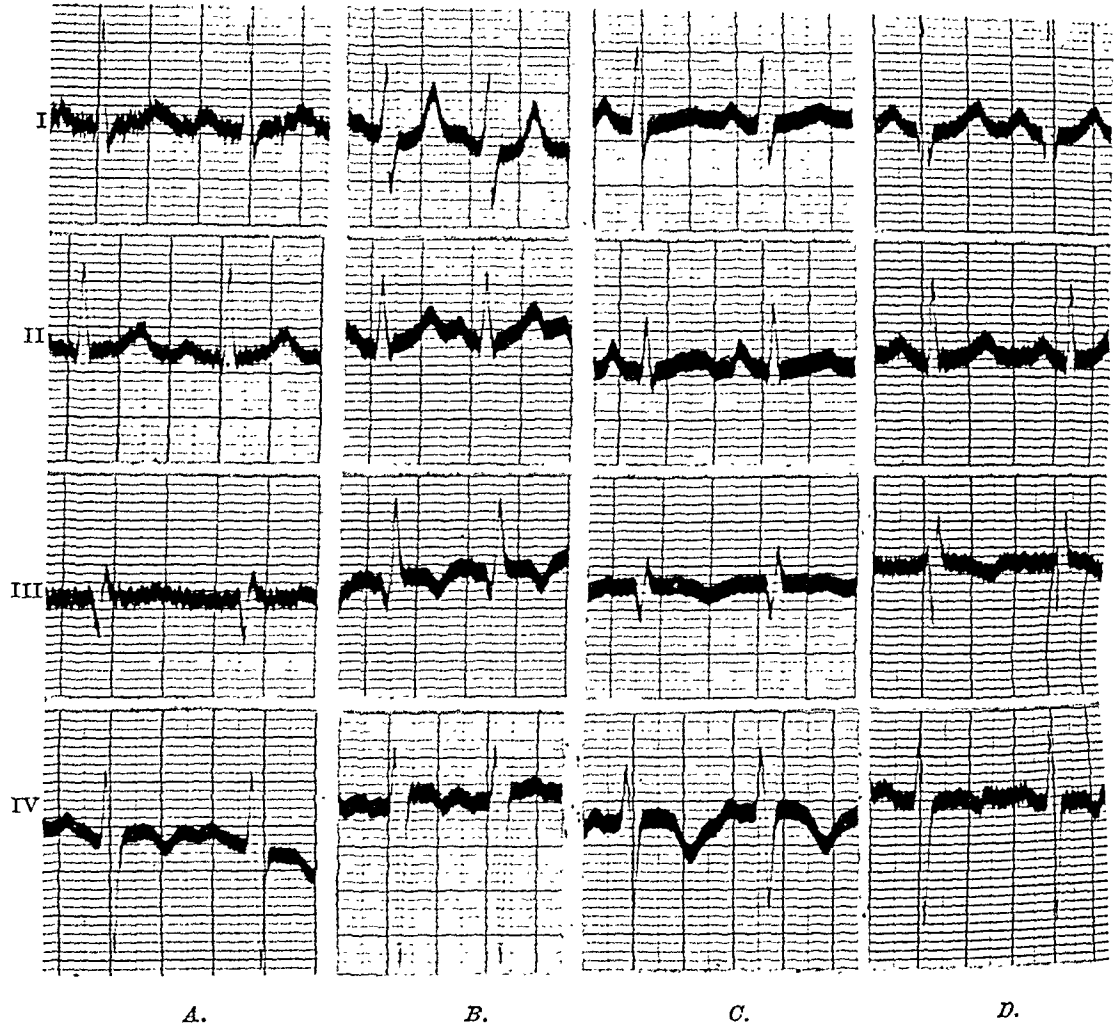


Fig. 7.—Case 7, L. S. A. May 2, 1938, 60 hours after first attack. B. May 18, 1938, 5 hours after attack of dyspnea, collapse, and side pain. C. May 23, 1938, clinically improving. D. April 2, 1941, no attacks since May, 1938.

The course of her illness from this date was very stormy. She had a series of seven attacks characterized by sudden onset of pain in either the right or left side of the chest, severe dyspnea and tachycardia, and, in addition, a fall in blood pressure. Hemoptysis occurred at intervals. The periods between the attacks were very variable, at times four days, at other times, ten days. The patient became extremely apprehensive, for she did not know at what hour she might be seized by another frightening attack of severe dyspnea, cyanosis, and collapse. Confirmatory evidence of the pulmonary involvement was obtained by numerous detailed studies on this patient. The electrocardiograms (Figs. 7-B and C) at first indicated strain on the right side of the heart and the state of acute cor pulmonale. Later, as the patient improved, the right axis deviation abated. During her hospital stay no physical signs of phlebitis were found.

Six months later she was well. Her heart was normal in size, and there were no murmurs. The blood pressure was 135/95. Almost three years after her discharge from the hospital, an electrocardiogram (Fig. 7-D), taken in the upright position, showed normal rhythm and a rate of 105. Right axis deviation was not present. Lead III was inverted, and there was slight inversion of the T wave in Lead IV. She looked well and had no complaints. She was moderately obese, and her heart was transversely placed.

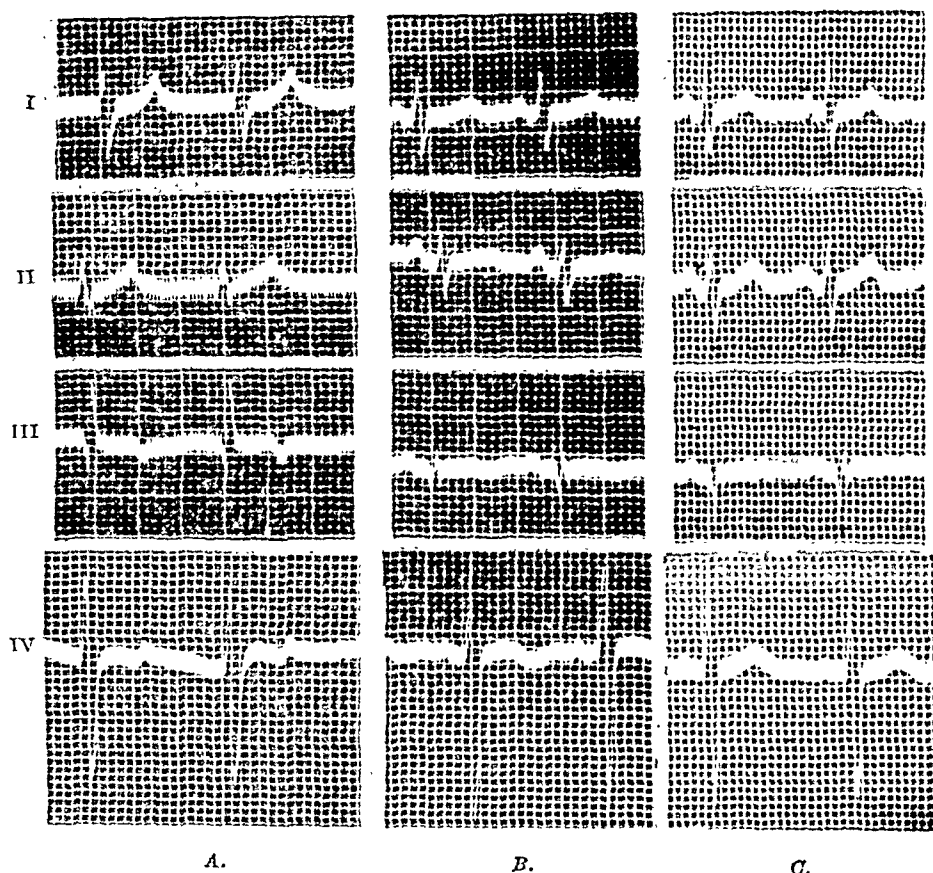


Fig. 8.—Case 8, C. C. A. October 3, 1938, 16 hours after first attack. B. October 7, 1938. C. March 3, 1941.

CASE 8.—C. C., a 52-year-old man, entered a hospital on September 21, 1938, where cholecystectomy and appendectomy were performed under spinal anesthesia on the following day. Convalescence was uneventful except for an unexplained, slight fever of 99° to 100°. On the tenth postoperative day, October 2, when he “dangled” for the first time, he was suddenly seized with an attack of breathlessness and substernal heaviness. He became pale, cold, and clammy, his heart rate was 140 and his pulse of poor quality, and his blood pressure was 70/60. Examination of his chest showed nothing abnormal. His heart was not enlarged, the sounds were poor, and the pulmonary second sound was not accentuated. His neck veins were not visibly distended. His leg veins appeared normal. On the sixteenth, twentieth, and twenty-sixth postoperative days he had similar but less severe attacks, during which he expectorated bloody sputum. He was discharged, symptom-free, on November 2, 1938.

An electrocardiogram on October 3 (Fig. 8-A), sixteen hours after the first attack, showed normal rhythm, a rate of 100, and right axis deviation. A deep S wave was present in Lead I. In Lead III a Q wave was present, and the T wave

was small but sharply inverted. The T wave in Lead IV was diphasic. A tracing (Fig. 8-B) four days later, on October 7, 1938, the fifteenth postoperative day, showed normal rhythm, a rate of 100, and a tendency towards low voltage. The degree of right axis deviation was less than in the first record. The depth of the Q wave and the inversion of the T wave in Lead III were much diminished. In Lead IV the T wave showed definite, but shallow, inversion. A subsequent tracing (Fig. 8-C), on March 3, 1941, showed normal rhythm and a rate of 95. An S wave persisted in Lead I. In Lead II the T wave was normal and in Lead IV the T wave had become upright.

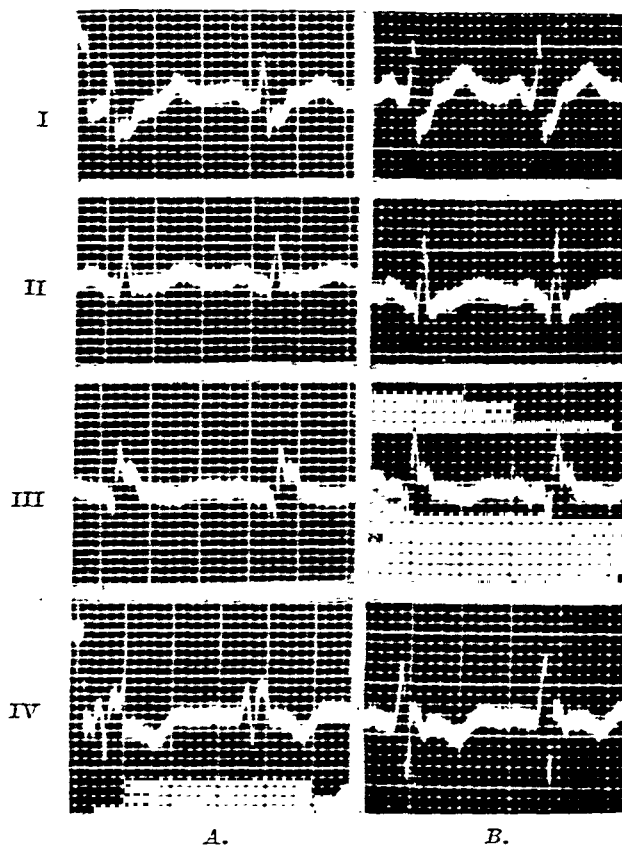


Fig. 9.—Case 9. M. C. A. March 5, 1940, 8 hours after second attack. B. April 28, 1940, approximately 7 weeks after last attack.

CASE 9.—M. C., a 60-year-old woman, entered the hospital February 23, 1940, a few hours after a fall. She was found to have a fracture of the neck of the left femur. On March 1, the hip was nailed under spinal anesthesia. Prior to this time there had been no symptoms suggestive of cardiac or pulmonary disease. Two days after the operation the patient complained of a sudden pain at the lower end of the sternum; this pain was of short duration. It was followed on the same day by the expectoration of bloodtinged sputum and occasional clots. Her temperature before and after the operation varied from 99° to 100° F. Physical examination on March 3 showed that the heart was normal. A few crackling râles were heard in the upper part of the chest and axilla on the left side. On the fourth postoperative day, March 5, she experienced a sharp pain at the right costal margin, made worse by deep breathing and relieved by a binder. The temperature and pulse and respiratory rates were increased. The patient was apprehensive, cold, and clammy. A pleural friction rub was heard in the painful area, and it was observed that the pulmonic second sound was accentuated.

An electrocardiogram (Fig. 9-A), taken eight hours after this second attack,

showed right bundle branch block, with a wide S wave in Lead I, and a rate of 105. There was a gradual ascent of the S-T segment in Lead II. There were a Q wave, splintering and slurring of the QRS complex, and an inverted T wave in Lead III. The R wave in Lead IV was upright, and the T wave was deeply inverted. A roentgenogram of her chest showed an area of increased density in the right lower portion. Again on the ninth and eleventh postoperative days, sharp pains occurred in the left side of the chest. Gradually she improved and did well for six weeks. Then once again she experienced pain in the right side of her chest; it lasted this time for twenty-four hours, and was followed by expectoration of blood. At this time she complained of soreness and swelling in the lower part of the left leg.

An electrocardiogram (Fig. 9-B), taken April 28, 1940, showed persistence of the right bundle branch block. The S-T segment in Lead II was isoelectric, and the T wave was upright. The T wave in Lead III was only slightly inverted. There is no evidence available to indicate whether the bundle branch block appeared as the result of the acute right ventricular dilatation or whether it existed prior to her accident. She improved considerably, and, one year later, could walk well without discomfort. She had no further chest pain.

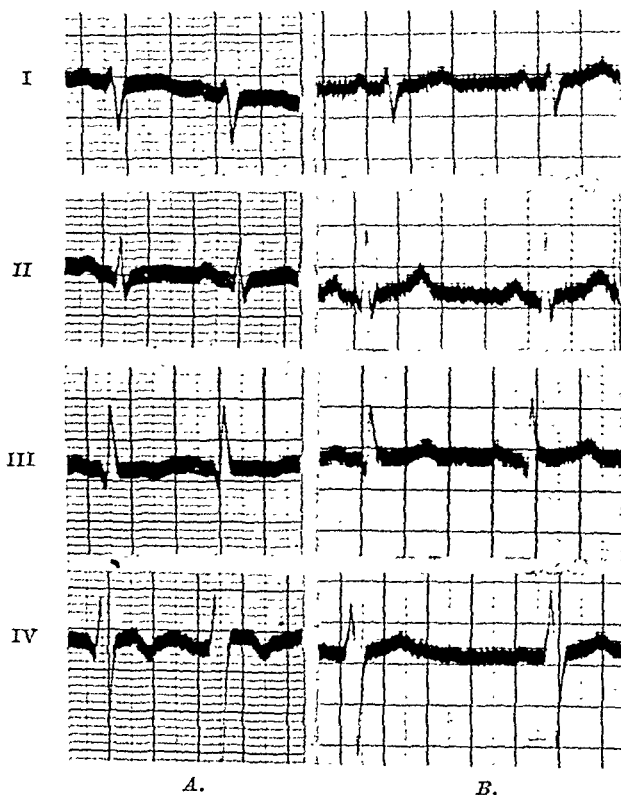


Fig. 10.—Case 10, I. W. A. May 10, 1939, 4 days after first attack. B. August 5, 1941.

CASE 10.—I. W., a single, 27-year-old man, had a typical attack of acute appendicitis on April 15, 1939, and was subjected to an appendectomy on the following day. His convalescence was satisfactory until May 6, when he experienced severe substernal pain, with collapse and dyspnea, while sitting in a chair. On physical examination he was ashen, sweating profusely, and had cold extremities, with peripheral cyanosis. His cervical veins appeared full, but not markedly distended. The heart rate was 125, and the blood pressure was 80/40. The leucocyte count was 13,500. Pulmonary embolism was suspected, and a constant intravenous

infusion of heparin in physiologic salt solution was started at once. The clotting time was kept at approximately forty minutes. No evidence of peripheral phlebitis in his legs was discovered. Neither cough, dyspnea, nor pain was present twenty-four hours after the attack. A roentgenogram of the chest on May 7 showed no evidence of disease. On May 10 another roentgenogram of the chest revealed a large area of hazy density, rounded in the lateral view, at the base of the right lung in the costophrenic angle, and a small dense area in the base of the left lung. These were interpreted as the result of infarction.

An electrocardiogram on May 10 (Fig. 10-A) showed normal rhythm, a rate of 120, and marked right axis deviation. The T waves were low in Lead I and Lead II, slightly inverted in Lead III, and inverted in Lead IV. A Q wave was present in Lead III.

The heparin was stopped arbitrarily on May 13. An electrocardiogram on this date showed normal rhythm and a rate of 115. The right axis deviation was less marked, and the T waves in Lead I and Lead II were upright. In Lead III a small Q wave and an inverted T wave were seen. In Lead IV the T wave was definitely inverted. On May 16 the consolidated area in the base of the left lung appeared roentgenographically as two fairly well-defined areas, both of which were believed to represent infarcts. Three days later (May 19) the patient complained of stiffness in his left calf and thigh. It was normal in appearance, and its girth was not increased. The leucocyte count was 9,600. The temperature and pulse rate were normal. On May 20, he complained of pain in the left calf. His temperature rose to 100° and his pulse rate to 90. There was edema of the entire leg; its girth was now uniformly greater than the right. Homan's sign, namely, the induction of pain in the calf region by dorsiflexion of the foot, became positive. A diagnosis of acute thrombophlebitis of the deep veins, with evidence of superficial phlebitis in the lesser or short saphenous vein, was made. Ligation of the femoral vein distal to the junction of the vena profunda femoris was performed. The long saphenous vein was ligated separately. Moderate swelling of the thigh was present for forty-eight hours, and then diminished. The pain in the calf disappeared six days after operation, and he was walking on the eleventh postoperative day.

Eleven months later he was quite well, and had had no recurrence of pulmonary embolism. A follow-up electrocardiogram on August 5, 1941 (Fig. 10-B), showed sinus arrhythmia, a rate of 70 to 80, and right axis deviation, which, although somewhat decreased, had persisted. A small Q wave was still present in Lead III. All of the T waves were upright.

REVIEW OF THESE TEN CASES

In this series there were three cases (1, 6, 9) in which pulmonary embolism followed bone injuries in women over the age of 60, with one fatality. There were three cases of postoperative embolism (3, 8, 10); two of these patients were in the third decade, and there was one fatality. Three patients (4, 5, 7) presented pulmonary symptoms from the beginning of their illness, and one (2) had varicose veins and phlebitis. In the miscellaneous group of four patients, there were three fatalities. Nine patients had two or more attacks of infarction. The tenth patient had only one. He was probably saved from further attacks by the ligation of his femoral vein. All five fatalities were caused by a major obstruction, which was the second attack in four cases, and the third in one.

The electrocardiogram gave the first suggestive laboratory evidence of the correct diagnosis in three cases (4, 5, 7); in the others, the electro-

cardiographic changes were confirmatory of the clinical diagnosis. Follow-up studies revealed an almost complete return to the normal pattern in Cases 1 and 6, and a partial return in Cases 4, 7, 8, and 10. Among the survivors, right axis deviation persisted in three cases (8, 9, 10).

Peripheral thrombosis or phlebitis in the lower extremity was present or suspected clinically in five cases (2, 4, 6, 9, 10). Thrombosis of the popliteal vein was found at post-mortem examination in two cases (1 and 4), and in the prostatic venous plexus in one (5). Venous thrombosis in the legs was not suspected or discovered in three patients (3, 7, 8), two of whom had acute attacks on the eighth and tenth days post-operatively, respectively. Four patients (2, 4, 5, 7) were ambulatory when they had their first attack. The remaining six had been in bed at least six days. The onset was not clearly acute in Cases 4 and 5. A wide S wave in Lead I occurred in Cases 3, 4, 5, 8, 10, and (1)9, and may be comparable to the transient right bundle branch block reported by Durant, et al.⁹

OTHER CASES OF PULMONARY EMBOLISM

To evaluate the electrocardiographic changes in pulmonary embolism, a series of ninety-two other patients with this condition who had been seen in the wards of the Massachusetts General Hospital and in private practice was studied. Approximately 50 per cent of these patients had electrocardiograms taken within twenty-four hours of the pulmonary embolism. No patient was included who did not have an electrocardiogram taken within ninety-six hours of the attack. We found that only about one case in six of pulmonary embolism had been studied electrocardiographically.

The diagnosis was confirmed by autopsy in forty-two cases. In the remaining fifty cases, the clinical diagnosis was adequately supported by physical and laboratory evidence. The cases were analyzed in two groups, namely, those in which the diagnosis was confirmed at autopsy, and those in which the diagnosis was only clinical. Each group has been subdivided into (a) cases in which the features of shock predominated at the onset of the attack, and (b) cases in which signs and symptoms of pulmonary infarction, without shock, characterized the clinical picture.

Forty-Two Autopsy Cases.—Thirty-nine were cardiac patients (hypertensive and/or coronary heart disease, twenty-four; rheumatic heart disease with mitral stenosis, ten; miscellaneous, five). Many of these showed multiple pulmonary infarcts at autopsy.

(a) In thirteen of the forty-two cases the clinical features of *shock* predominated at the onset of the attack. Of these cases, organic heart disease occurred in eleven, and, in almost all, coronary disease was the etiologic factor (there were no cases of rheumatic heart disease in this group). No change in the already abnormal electrocardiograms occurred after the attack in six of this group of eleven. Of the remaining

five cardiac patients, one showed all the characteristic features of the acute cor pulmonale pattern except right axis deviation; another exhibited a temporary shift from slight left towards right axis deviation, and two others showed depression of the S-T segment in Lead I and in Lead II (digitalis influence was excluded) as the principal electrocardiographic alterations. The remaining cardiac patient developed auricular fibrillation coincident with the attack.

The two patients without heart disease in this group were of considerable interest. Auricular flutter was precipitated in one, and a tendency towards right axis deviation (small S wave in Lead I) developed in the second. In common with four cardiac patients (three of whom showed no electrocardiographic change, whereas the fourth developed auricular fibrillation), these patients had only a few small pulmonary infarcts at autopsy. Certainly the mechanical factor of obstruction in the pulmonary arterial bed was minimal in these cases.

(b) In twenty-nine of the forty-two cases, *the signs and symptoms of pulmonary infarction*, without shock or collapse, predominated clinically. Complicating factors, which of themselves could modify the electrocardiogram, were present in all cases in this group. Organic heart disease was present in twenty-eight cases, and full therapeutic doses of digitalis were being administered when the electrocardiogram was made in the remaining one. Nevertheless, temporary changes that were believed to be significant evidence of some degree of acute cor pulmonale occurred in ten cases. In three additional cases, auricular fibrillation developed. In each case the abnormal rhythm was apparently precipitated by a small embolus. The electrocardiographic changes which occurred included, first, the temporary appearance of a small S wave in Lead I or the temporary disappearance of previously existing, slight, left axis deviation; and, second, a depression of the S-T take-off and segment in Lead II, and less frequently in Lead I. These alterations were correlated with significant thrombotic obstruction in the pulmonary arterial bed at autopsy. Large terminal emboli, if present, were excluded. Temporary deviation of the electrical axis towards the right was the most common electrocardiographic alteration.

Lead IV-F was available in thirty-one of the forty-two cases. Inversion of the T wave, with an upright R wave, occurred in eight cases, and, in three cases, a diphasic appearance of the T wave occurred. Five patients had an abnormal T wave prior to the pulmonary embolism. In the remaining fifteen cases the T wave was upright.

We believe that those patients who developed temporary deviation of the electrical axis towards the right or a depression of the S-T segment in Lead II or in Lead I actually had some degree of acute cor pulmonale at the time the electrocardiogram was made, even though the clinical manifestations of the condition were not then apparent.

Fifty Cases of Pulmonary Embolism, Without Autopsy.—Organic

heart disease was present in at least twenty-seven of these cases, i.e., coronary heart disease in twenty-one, and rheumatic heart disease in six. The electrocardiographic changes mentioned refer to those recognized after an attack of pulmonary embolism.

(a) There were sixteen cases (seven were cardiac patients with coronary artery disease and/or hypertensive heart disease) in which the signs and symptoms of *shock* predominated at the onset of the attack. No patient showed all of the features of the typical electrocardiographic pattern of acute cor pulmonale. Three patients with hypertensive heart disease developed the pattern except for right axis deviation. Two others showed electrocardiographic changes which were deemed significant evidence of some degree of acute cor pulmonale. These included a small S wave in Lead I and a low take-off of the S-T segment in Lead I, or in Lead II, and a Q wave and inversion of the T wave in Lead III. Variable, slight inversion of the T wave in Lead IV accompanied these alterations in the limb leads.

Lesser, temporary, electrocardiographic changes occurred in four cases. They appeared individually, and perhaps indicate that a slight degree of acute cor pulmonale was caused by the pulmonary embolus. These alterations were the appearance of a small S wave in Lead I, a low S-T take-off and segment in Lead II or in Lead I, and inversion of the T wave in Lead IV. Shallow inversion of the T wave in Lead IV occurred as an isolated abnormality in two additional cases. This is of questionable diagnostic significance, but is consistent with a mild, transient degree of acute cor pulmonale. Since Lead IV-F was employed, it can be said that the chest electrode may have been on the border of the right ventricle, or was so influenced by it, that an indeterminate T wave resulted.

(b) Thirty-four patients presented the *clinical signs and symptoms of pulmonary infarction*, without shock or collapse. Of these, twenty had heart disease. No typical electrocardiographic pattern of acute cor pulmonale was found. Small changes did occur in seven cases, including a small S wave in Lead I and a low take-off of the S-T segment in Lead I or Lead II. Auricular flutter developed in one patient coincident with the attack. There were no electrocardiographic alterations in the remaining twenty-six cases. This latter group included those patients whose previously abnormal records were unchanged by the attacks, and those whose electrocardiograms were still normal after pulmonary embolism occurred.

Summary of This Series of Ninety-Two Cases.—Co-existent heart disease was present in sixty-nine of these cases. In twenty-nine, symptoms of shock predominated at the onset, and, in sixty-three, the signs of pulmonary infarction without shock or collapse were predominant. Electrocardiographic changes which were considered suggestive of a minor degree of acute cor pulmonale were present in sixteen of the former

and in seventeen of the latter. The onset of auricular fibrillation was observed in four cases, and auricular flutter in two cases, in this series. Many cases of pulmonary embolism in the records were not studied electrocardiographically, and in others no electrocardiogram was taken until several days after the attack occurred. We believe, on this account, that the true frequency of helpful electrocardiographic changes after pulmonary embolism is probably greater than our figures indicate.

DISCUSSION

The terms "pulmonary embolism" and "acute cor pulmonale" are not synonymous. Not every patient with pulmonary embolism develops acute cor pulmonale, and hence the typical electrocardiographic changes do not always appear. If acute right ventricular strain were caused by an embolus, an electrocardiogram taken within a few hours of the onset of symptoms might be expected to show evidence of it. The degree of mechanical obstruction in the pulmonary circulation and, possibly, certain reflexes affecting the pulmonary vascular bed influence the length of time during which this evidence is manifested. The anoxia, and possibly also reflex coronary constriction, secondary to the pulmonary embolism, may perhaps act as additional factors to favor the development of the right ventricular dilatation of acute cor pulmonale, and may in themselves even influence the electrocardiogram.

During this study two interesting observations were made: (1) Electrocardiographic evidence suggestive of acute cor pulmonale was found after the occurrence of pulmonary embolism when the clinical signs of the condition were not apparent, and (2) symptoms of shock and collapse may predominate even with small emboli. Of the six cases in which this occurred, electrocardiographic signs of mild, acute cor pulmonale were present in only one. Before the degree of acute cor pulmonale which may exist temporarily in similar cases can be ascertained, further electrocardiographic observations must be made soon after the onset of symptoms.

Some factors which may modify the appearance, or even obscure the features, of the typical pattern are: (1) deviations from the normal caused by pre-existing heart disease; (2) the degree of mechanical obstruction to the pulmonary circulation; (3) the length of the interval between the attack and the taking of the electrocardiogram; (4) the presence of abnormal conditions which of themselves alter the electrocardiogram, e.g., toxic states, digitalization; and (5) the presence of abnormal rhythms.

Apparently, acute cor pulmonale may occur in varying degrees of severity. In the most marked cases there are the signs of dilatation of the right auricle and ventricle and the typical electrocardiographic pattern previously described; the lesser grades may or may not cause transient clinical signs, and may produce only temporary electrocardiographic changes of significance, namely, a tendency of the electrical axis

to deviate towards the right, evidenced most commonly by a small S wave in Lead I, or a low take-off of the S-T segment in Lead I or in Lead II, or a Q wave and inversion of the T wave in Lead III, or a negative T wave in Lead IV. In some instances the degree of right axis deviation may be slight; in others, the T wave in Lead IV may be upright. When the possibility of acute cor pulmonale arises, we recommend the use of multiple chest leads. The T wave is most likely to be inverted when the precordial electrode is over the right ventricle. Lead IV-F sometimes records the electrical potential from the right ventricle and sometimes from the left, more especially if left ventricular hypertrophy exists. This is probably very important in actual practice. Chest lead positions 2 and 3 should be explored when in doubt, that is, in the fourth intercostal space just to the left of the sternum, and midway between that point and the midclavicular line on the line from point 2 to the cardiac apex. Normally the T wave is upright in these two precordial leads, but in the case of the acute cor pulmonale it is inverted (more definitely than in the routine Lead IV).

Many tracings record only the tachycardia associated with the embolism. They are included in our study as those without significant electrocardiographic alterations, and classified as without change. The presence of organic heart disease, with an abnormal electrocardiogram, as in mitral stenosis or coronary heart disease with myocardial anoxemia—pulmonary infarction is a frequent complication in these cases—often limits the diagnostic value of the electrocardiogram in a suspected state of acute cor pulmonale.

The onset of abnormal rhythms and various types of heart block has been reported as a result of pulmonary embolism. Four cases of auricular fibrillation and two of auricular flutter were observed in our series. Five examples of increased duration of the S wave in Lead I have been mentioned above.

In evaluating the electrocardiogram of a patient who is suspected of having acute cor pulmonale as a result of pulmonary embolism, it is important to know how much time elapsed between the onset of the attack and the taking of the electrocardiogram. If the obstruction to the pulmonary circulation is small or is overcome soon after its occurrence, the embarrassment of the right ventricle will pass off rather rapidly. An electrocardiogram taken within a few hours of the attack may therefore afford the only means of recognizing it, for such signs as an S wave in Lead I, or an inverted T wave in Lead IV, often persist after the physical signs, if there were any, have disappeared. However, even these signs may have disappeared completely within twenty-four hours of the attack. This evidence can be available before roentgenologic signs of pulmonary infarction develop.

Many authors confirm the fact that coronary occlusion has been commonly confused with severe, acute cor pulmonale. This has been amply borne out in our experience. Several observers have mentioned the

clinical differential diagnosis and have indicated the important diagnostic value of the electrocardiogram. However, the electrocardiographic features may be confused in both of these conditions when the changes are atypical or equivocal. An accurate history and a careful appraisal of the physical signs remain of major importance in establishing the correct diagnosis. Serial electrocardiographic studies are then helpful in evaluating the status of the heart.

It is, incidentally, of great importance to recognize the fact that either condition may complicate or more or less set off the other (pulmonary embolism from stasis during convalescence from myocardial infarction, or myocardial infarction in a person with considerable coronary disease whose coronary circulation is decreased by pulmonary embolism); there

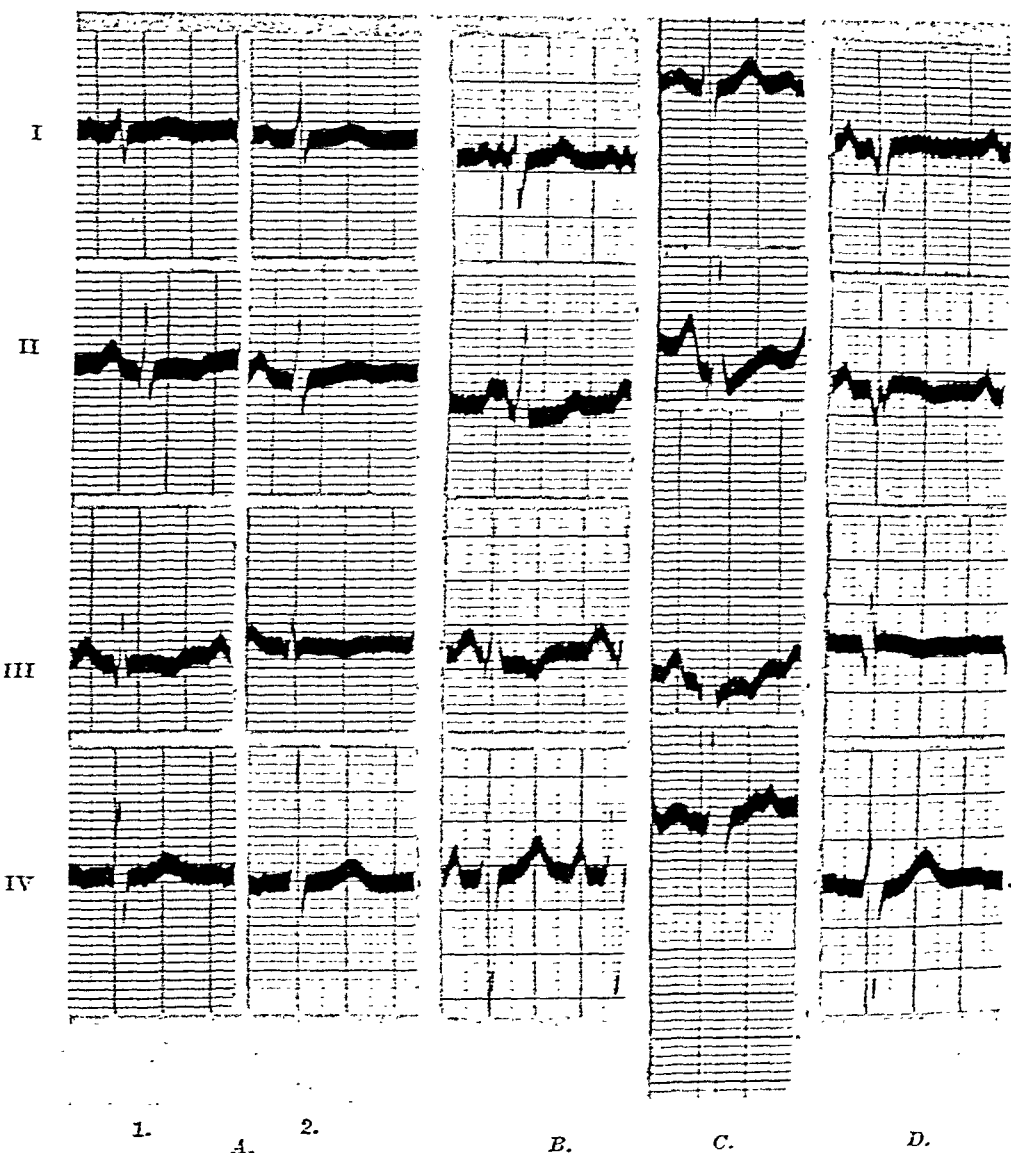


Fig. 11.—A, St. L. 1. Electrocardiogram of a normal heart in a patient of asthenic build. September 10, 1941. Sitting position. 2. September 11, 1941. Recumbent position. B, N. I. Electrocardiogram of a patient with mitral stenosis. August 25, 1941. C, O. M. Electrocardiogram of a patient with Tetralogy of Fallot. November 12, 1926. D, J. A. W. Electrocardiogram of a patient with recent posterior myocardial infarction. April 28, 1942.

then may be a double effect of the two conditions on the electrocardiogram. The complication, nay, even the precipitation, of one condition by the other has not been taken adequately into account in the past. Sometimes the anoxemia resulting from pulmonary embolism may produce transient changes in the electrocardiogram which may simulate somewhat, but not exactly, acute cor pulmonale, without the more persistent changes found with actual myocardial infarction. It is, of course, the posterior and not the anterior myocardial infarct or anoxic state that superficially resembles acute cor pulmonale in its effect on the electrocardiogram.

In three (4, 5, 7) of our ten cases, acute cor pulmonale was not considered until it was suggested by the electrocardiogram. Other examples very likely pass unrecognized, as almost happened in these cases. The large mortality among these patients and the discovery of thrombosed veins in their extremities suggest that timely diagnosis and operation on the affected veins should be the physician's goal. Prophylactic leg exercises, combined with more attention to the leg veins by the physician, and widespread recognition of the varied manifestations of pulmonary embolism should lead to a sharp decrease in the incidence of fatal pulmonary emboli, more especially among patients confined to bed. Bland thrombosis of the veins, the so-called phlebothrombosis, may baffle the most competent physician, and deliver a lethal embolus to the pulmonary circuit before it is recognized. In this connection the introduction of venography has been of considerable importance. With this technique the patent venous channels are outlined by a radiopaque dye, such as diodrast. Venous obstruction, especially in the deep veins of the leg, may thus be revealed. The appropriate veins can then be ligated and the danger from pulmonary embolism considerably reduced. Experience with venography suggests that discrimination in the selection of patients and improved technique will lessen the incidence of complications, such as local phlebitis at the site of injection.

A few additional electrocardiograms (Fig. 11, *A, B, C, D*) are herein presented, with brief clinical notes, because of their superficial similarity in some respects to the acute cor pulmonale pattern. They show *normal* rhythm and a rate of 100 or faster, with slight to moderate right axis deviation. A Q wave was present and an inverted T wave was often seen in Lead III. The T wave in the chest lead was upright. This group included asthenic persons with rapid heart rates, and persons with mitral stenosis, certain forms of congenital heart disease, and posterior myocardial infarction. They emphasize the fact that it is important to possess clinical knowledge of the patient in order to evaluate the record accurately.

SUMMARY

Ten patients with acute cor pulmonale, without underlying heart disease, five of whom died (three had post-mortem examinations), are

presented with their electrocardiograms to corroborate the observation that there is a typical electrocardiographic pattern in acute cor pulmonale; it is characterized by right axis deviation with a prominent S wave in Lead I, a depressed S-T segment in Lead II and often in Lead I, a Q wave and an inverted T wave in Lead III, and a diphasic or an inverted T wave in Lead IV-F. An upward convexity of the S-T segment in Lead III is common; an elevation of the S-T take-off in this lead occurs in a few cases. The cases were selected so that other factors which of themselves could have modified the electrocardiogram were excluded.

The electrocardiographic changes in an additional series of ninety-two cases of pulmonary embolism were reviewed. Co-existent heart disease occurred in sixty-nine. In twenty-nine cases symptoms of shock predominated; in sixty-three the signs of pulmonary infarction without shock or collapse predominated. Electrocardiographic changes that were considered indicative of acute cor pulmonale were present in sixteen of the former group, and in seventeen of the latter. In other words, the electrocardiogram gave indication of some degree of acute cor pulmonale in a little more than one-half of the cases when shock predominated, in a little less than one-quarter of the group without shock, and in about one-third of the entire series, including those patients who had abnormal electrocardiograms as a result of heart disease.

It is emphasized that "pulmonary embolism" and "acute cor pulmonale" are not synonymous terms. It appears that varying degrees of acute cor pulmonale occur, and that the electrocardiogram provides a means of evaluating the status of the heart, especially when clinical signs indicative of right-sided heart strain are not obvious.

It is our belief that anoxemia produced by a pulmonary embolus may cause infarction in cardiac muscle which is already the seat of severe coronary artery disease. When this occurs, the electrocardiographic changes are confusing and atypical.

Death is often caused by a second or third embolus. Prophylactic leg exercises, venography, and, if indicated, ligation of the femoral vein should reduce the incidence of fatal pulmonary emboli.

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ADDENDUM

Since the preparation of this paper an important article has been published by James Currens (The Electrocardiogram in Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* 17: 502, 1942). In an endeavor to shed more light on the problem, careful microscopic examination was made of the hearts in thirty cases of pulmonary embolism, with section of the coronary arteries every 5 mm. throughout their course, and, in addition, at least six sections from right and left ventricles of each heart. In five cases, recent infarction of the right or left ventricle was found, in one of which there was recent thrombosis of the right coronary artery, but in the remaining four no demonstrable occlusion of the coronary arteries. Currens writes as follows: "In appraising the electrocardiographic changes during suspected pulmonary embolism it should be borne in mind that no one electrocardiographic abnormality is consistently present in pulmonary embolism"; and in summary, he states: "The cause for the electrocardiographic changes in pulmonary embolism is considered, and strain on the right ventricle seems to be the dominant factor. The presence of a pulmonocoronary reflex following pulmonary embolism is difficult to prove, and it seems likely that any compromise in the coronary circulation is best explained by shock and an increase in pressure in the right side of the heart. The decrease in blood flow to the right ventricle from a decrease of arterial pressure gradient, plus an increase in work of the right ventricle may account for the occasional association of angina pectoris with pulmonary embolism. Evidence is presented to suggest that asphyxia does not appreciably affect the electrocardiogram in pulmonary embolism. The electrocardiographic pattern in pulmonary embolism is variable and the value of the precordial leads is stressed."

ON THE AMOUNT OF, AND CHANGES IN, THE RESIDUAL BLOOD OF THE HEART

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TODAY our knowledge of the capacity of the different heart chambers during life is extremely imperfect. On the other hand, as regards the volume of the whole heart, there are, in the earlier literature, accounts of a number of investigations carried out on autopsy material, such as those of Beneke,¹ Müller,² and Henle,³ but these comprise data on only the weight of the muscular substance of the heart (Müller), or the volume of the muscular substance (Beneke). Beneke found that the adult male heart has a volume of about 300 c.c., which is in good agreement with Müller's statement that the weight amounts to about 300 Gm.

During recent years, Kahlstorf,^{4, 5} Nylin,⁶ Lysholm, Nylin, and Quarnå,⁷ and Liljestrand, Lysholm, Nylin, and Zachrisson⁸ have made contributions toward elucidation of the volume conditions of the heart in vivo. The last-mentioned authors found that the normal volume of the heart in seventy healthy adults (students) amounted, on an average, to 700 c.c. Judging from Beneke's work, which indicates that the muscular substance has a volume of about 300 c.c., this would imply that the capacity of the heart cavities would amount to about 400 c.c. (700 - 300) altogether. We do not at present know with certainty whether this is the case. For reasons which are easily understood, the volume of the heart cavities is difficult to define, and the measurements which have been made in vitro are only of limited interest. As far as can be ascertained, only Hiffelsheim and Robin,⁹ and, considerably later, Hochrein,¹⁰ arrived at any conception as to the volume of the heart cavities. Hiffelsheim and Robin made post-mortem wax casts of the four cavities and calculated their size by ascertaining the displacement of the wax casts. From five normal persons in Hiffelsheim and Robin's series I have calculated that the total volume of the four cavities of the heart averaged 617 c.c. On the other hand, Hochrein gives a mean value of 561 c.c., calculated from thirty cases. Hochrein's technique differed from Hiffelsheim's, in that he ascertained "the capacity," i.e., the volume of the heart cavities, by filling the cavities under a water pressure of 8 cm. and measuring the amount of water required. If 300 c.c. for the tissue of the heart is added to Hiffelsheim and Robin's and Hochrein's mean values of the total capacity of the heart, the estimated volume of the heart for the respective authors amounts to 917 c.c. and 861 c.c.

To what degree the heart is emptied during systole has been discussed by several authors. Rollett¹¹ says: "Im Leben entleeren sich beide

Ventrikel gleichzeitig und gleich oft in der Zeiteinheit und zwar bis zum Verschwinden ihrer Höhlung." On the other hand, Chauveau and Faivre,¹² Roy and Adami,¹³ and Starling¹⁴ have assumed that the heart does not expell the blood completely during systole. It may probably be assumed that, during life under physiologic conditions, and more especially under pathologic conditions, the heart is not completely emptied of blood during systole, but that larger or smaller, nay, even considerable, quantities remain in the heart cavities; in other words, there is a certain amount of residual blood.

At the present time the stroke volume of the heart can be fairly exactly ascertained by the gas methods, at least in healthy persons. Nylin¹⁵ found that it amounted to a mean value of 71 c.c. in healthy adults in the recumbent position; the heart volume of these subjects, as ascertained roentgenologically, averaged 843 c.c. Unfortunately, in this work it was not stated in which phase of the heart beat the estimations were made, but it is probable that, in view of the long exposure times, they were made during diastole. If the volume of the tissue of the heart in these experiments is estimated as 300 c.c., this would imply a diastolic capacity volume for the whole heart of about 540 c.c. If this value is decreased by twice the stroke volume (142 c.c.), the amount of residual blood in the recumbent position would normally amount to about 400 c.c. and, in the standing position, to only about 200 c.c.

Under certain pathologic conditions, and especially in cases of advanced cardiac insufficiency, it is generally known that there is considerable enlargement of the heart which cannot be due entirely to hypertrophy of the musculature, but rather to dilatation of the heart. From this it follows—since the stroke volume does not increase, but decreases—that the quantity of residual blood increases, and, in many cases, must become extremely large. Of the volume of these quantities of residual blood in cardiac insufficiency we know practically nothing.

RADIOLOGIC ESTIMATIONS OF CHANGES IN HEART VOLUME (CHANGES IN RESIDUAL BLOOD)

With the introduction of the roentgenologic method of estimating the heart volume by Kahlstorf, Lysholm, Nylin, and Quarnå, Liljestrand, Lysholm, Nylin, and Zachrisson, and Jonsell,¹⁶ possibilities of obtaining a more objective measure of the size of the heart were created. Moritz,¹⁷ Binhold,¹⁸ Kahlstorf,¹⁹ Natvig,²⁰ Böhme,²¹ Nylin,^{22, 23} Liljestrand, Lysholm, and Nylin,²⁴ and Nylin, Sällström, and Ågren²⁵ have shown that the heart is subject to considerable volume changes, both physiologic and pathologic. The heart is considerably larger in the recumbent position than in the upright position. It is also subject to changes in size as a result of changes in intrathoracic pressure; this is shown in extreme form by the fact that, with Müller's test, the heart is consider-

ably larger than with extreme expiration and pressure, as in Valsalva's test. It has also been found that the heart is subject to a decrease in volume after pneumothorax has been induced. Muscular work also influences the size of the heart, in that the heart volume decreases after heavy muscular work. The above, mainly physiologic, changes in heart volume imply that the amount of residual blood undergoes considerable changes. These physiologic alterations in the amount of residual blood are summarized in Table I. Several of these particulars derive from a number of observations, and are the mean values; others comprise only single observations. As we see from the table, the changes in the quantity of the residual blood which occur with the transition from the standing to the recumbent position, and in the extreme conditions of Valsalva's and Müller's experiments, are very considerable, whereas those which take place during muscular work are of a much smaller order of magnitude.

TABLE I

PHYSIOLOGIC CHANGES IN THE AMOUNT OF RESIDUAL BLOOD OF THE HEART

1. Postural changes—mean increase in the heart volume in 11 healthy persons on changing from standing to lying position	269 c.c.
2. The effect of intrathoracic pressure—decrease in the heart volume with transition from MÜLLER's to VALSALVA's experiment	400 c.c.
3. The effect of muscular work—mean decrease in the heart volume in 12 healthy persons after heavy muscular work, in comparison with the volume before the work	35 c.c.

Under pathologic conditions the heart is subject to considerable changes in volume, which depend on the degree of decompensation. Comprehensive observations on this point have been collected in the course of years at the Seraphim Hospital. In 1939, Nylin, Sällström, and Ågren²³ reported that, of about one thousand estimations of heart volume made since 1933, at least one hundred showed more or less pronounced changes. From these investigations it emerges that the largest number of volume changes are met with in connection with variations in the degree of cardiac insufficiency. If repeated heart volume estimations are made in a cardiologic department, it will be found that such changes are common. As an example of extreme, reversible changes in the amount of residual blood intimately associated with the degree of decompensation, I shall cite one of my cases of mitral and tricuspid insufficiency. As the patient improved and the heart failure decreased, the amount of residual blood decreased by 400 c.c.; there was an increase of no less than 650 c.c. six weeks later, when severe decompensation had set in again. The patient did not recover from this attack of failure. At autopsy it was proved that an exudate in the pericardium, amounting to only 50 c.c., had not had any noteworthy influence on the heart volume. In cases of pronounced hypertension, when the blood pressure had decreased considerably after treatment, particularly con-

finement to bed, considerable decreases in the residual blood have been observed. In coronary disease, such as angina pectoris and coronary thrombosis, changes in the amount of residual blood of as much as 300 c.c. have been observed. In beriberi it has been proved that there is an increase in residual blood of 290 c.c. (Nylin²⁶). In a case of severe secondary anemia the decrease in the volume of the heart amounted to 350 c.c. when the blood was restored to normal. In a case of obesity, a decrease in weight of 40 kg. led to a decrease of no less than 360 c.c. in the heart volume. As is well known, myxedema is accompanied by dilatation of the heart, which recedes rapidly with thyroid therapy. I personally have no estimations of the decrease in residual blood in such cases, but Warburg²⁷ and others have published such observations.

TABLE II

PATHOLOGIC CHANGES IN THE AMOUNT OF RESIDUAL BLOOD OF THE HEART

1. Reversible changes which depend on the degree of decompensation	100—800 c.c.
2. Hypertension—single observations	180 c.c.
3. Coronary insufficiency, angina pectoris	330 c.c.
4. Coronary thrombosis—single observations	350 c.c.
5. Beriberi—single observations	290 c.c.
6. Anemia—single observations	350 c.c.
7. Obesity—single observations	360 c.c.
8. A. (a) Decrease in the heart volume in a case of unilateral pneumothorax	200 c.c.
(b) Decrease in the heart volume in a case of unilateral pneumothorax	125 c.c.
B. Decrease in the heart volume in a case of bilateral pneumothorax	350 c.c.

Table II shows these pathologic changes in the amount of residual blood. They are of great importance for an understanding of the pathophysiology of cardiac insufficiency. It is probable that the increase in the amount of residual blood, even in the incipient stages of cardiac insufficiency, constitutes a compensatory mechanism by increasing the length of the fibres and consequently the effectiveness of the heart muscle, in accordance with Starling's law. By means of observations on the changes in heart volume under both physiologic and pathologic conditions, possibilities have been created of measuring quantitatively, to a certain extent, the changes in the amount of residual blood.

POST-MORTEM HEART VOLUME ESTIMATIONS AND CALCULATION OF THE AMOUNT OF RESIDUAL BLOOD IN VIVO

It has already been pointed out that Hochrein and others before him made occasional post-mortem estimations of the volume of the heart cavities. Hochrein points out especially that the quantity of blood in the different cavities of the heart generally exceeds very considerably the stroke volume, so that, even under physiologic conditions during systole, the heart would not evacuate all its contents. As far as I can discover, there is practically no information about such estimations on

clinical material. On twelve mainly normal hearts, Kahlstorf made a comparison between heart volumes, as ascertained roentgenologically and by the displacement method, on the heart post mortem, and found extremely good agreement. In co-operation with Ture Petré, I made a series of estimations of the roentgenologic volume ante mortem and the post-mortem displacement volume, and obtained varying results. Sometimes the agreement was extremely poor, probably because of the fact that after death the heart undergoes a decrease in volume with rigor mortis. (These investigations have not yet been published.) In order to study more closely the amounts of residual blood during life, occasional investigations have been made in recent years at the Seraphim Hospital and the Sabbatsberg Hospital by means of roentgenologic volume estimations immediately before death. At a certain time after death another heart volume estimation was made, and, in immediate association therewith, at autopsy, all the vessels of the heart were ligated and the heart removed, after which its volume was ascertained by the displacement method. Then the heart cavities were opened and emptied of their blood, and the blood content of each cavity was measured. By this means it was possible (1) to control the roentgenologic volume estimations by the displacement method, and (2) to detect a post-mortem decrease in volume, and thus calculate approximately the total capacity of the cavities during life. More exact data on these investigations in two carefully studied cases are given below.

The first case was that of a 69-year-old man who for ten years had suffered from progressive cardiac insufficiency, associated with coronary sclerosis. He was treated on eight different occasions at the Seraphim Hospital. During the last few years the heart volume was constant, on the whole, at about 2,000 c.c., so that this was a case of *cor bovinum*. At the last visit to the hospital his insufficiency was refractory to all therapy, and the roentgenologic heart volume amounted to 2,500 c.c. Four and one-half hours after death another roentgenologic estimation of the heart volume was made, and showed the amazing decrease of 1,220 c.c. Twenty-four hours after death the heart volume was measured by the displacement method and found to be 1,250 c.c., which agrees well with the roentgenologic heart volume post mortem. The blood content of the cavities of the heart post mortem was measured and found to be 500 c.c. Thus, in all, the calculated quantity of residual blood during life—apart from the slight double stroke volume of about 100 c.c.—amounted in this case to no less than 1,750 c.c. ($2,500 - 1,250 + 500$).

The second case was that of a 44-year-old woman who, from the age of 7 years, had suffered from valvular disease, the cause of which was unknown. She was admitted to the Sabbataberg Hospital Aug. 14, 1940, with severe cardiac insufficiency and grave signs of stasis. She had all the symptoms of mitral stenosis and tricuspid insufficiency, with a positive venous pulse. The venous pressure was 34 cm. She had an enlarged liver and general anasarca, and also pronounced cyanosis. She was refractory to all therapy. She was kept alive only by administering pure oxygen through a Boothby respiration mask. She died August 28, two weeks after admission. The roentgenologic estimation ante mortem showed a heart volume of 2,400 c.c., i.e., 1,850 c.c. per m^2 of body surface; this was therefore an enormous heart in proportion to the small thorax. The configuration of the heart was remarkable. It might almost have been thought that pericarditis was

present, but this did not appear to be the case. A roentgenologic heart volume estimation was made post mortem, but unfortunately the sagittal projection was not successful. In the frontal projection, at least, the heart had decreased, although not very much, in both length and breadth post mortem. As in the preceding case, all the vessels were ligated at autopsy, and the volume of the heart, as estimated by the displacement method, was found to be 1,335 c.c. At autopsy, 150 c.c. of blood ran from the heart cavities. The pericardium contained 440 c.c. of fluid. Thus, the post-mortem volume of the heart, together with the blood which ran out and the pericardial fluid, amounted to 1,925 c.c., which is not inconsiderably less than the volume as ascertained ante mortem. It is possible that this discrepancy was real, and caused by changes in the quantity of the residual blood with the onset of rigor mortis. In addition, at autopsy the quantity of blood in the right auricle was measured and found to be 625 c.c.; the left auricle contained 290 c.c. The ventricles contained practically no blood. The volume of the heart tissue was 390 c.c. Thus the two auricles contained 915 c.c. at autopsy, and 150 c.c. had run out. Therefore, the amount of residual blood post mortem was 1,065 c.c. If it is correct in this case that, with the onset of rigor mortis, the heart decreased by 475 c.c. ($2,400 - 1,925$) this would imply that during life the amount of residual blood was 1,065 c.c. plus 475 c.c., or 1,540 c.c. Both the right and left auricles contained very considerable quantities of residual blood, and this was, for the most part, the cause of the configuration of the heart in the roentgenogram ante mortem. The cause of the enormous dilatation of the auricles proved, at autopsy, to be extreme mitral and tricuspid stenosis.

From these two examples it appears that the quantity of residual blood during life in certain cases of grave heart insufficiency may approach several liters. By means of roentgenologic ante- and post-mortem volume estimations, combined with estimations by means of the displacement method and measurement of the blood content of the different chambers of the heart post mortem, it has become possible to study more closely the amount of residual blood in different cases during life.

THE IMPORTANCE OF MEASURING THE CIRCULATION TIME IN ESTIMATING THE AMOUNT OF RESIDUAL BLOOD

The fundamental symptom of cardiac insufficiency when the patient is resting in bed is congestion of either the lungs or the vena cava area, or both. In estimating the degree of congestion in the vena cava area, the usual method is to measure the pressure in a vein of the arm; and, without going into further detail, I will only say that venous pressure normally amounts, at most, to 10 cm. of blood. Unfortunately, we have no method of measuring the pressure in the pulmonary veins. The only possibility at present of estimating objectively the presence and degree of lung congestion is by means of roentgenologic examination.

Blumgart and Weiss's²⁸ method of measuring the circulation time opened new possibilities for judging the degree of congestion. These investigators injected radium emanation into the vein of an arm. Then, by a special method, the time of arrival of the radium emanation in the right half of the heart was established, then in the left half, and finally in the arterial system, e.g., in an arm. The method was simplified later, and other test substances, such as decholin, saccharin, fluorescein, hista-

mine, lobeline, and magnesium sulfate were used. I employ a 20 per cent solution of decholin, which is injected into the vein of an arm, and the time which elapses after the injection until the patient becomes aware of a bitter taste is measured. In this way the circulation time from the vein of the arm by way of the right half of the heart, the lungs, and the left half of the heart out into the arterial system to the tongue, is measured. Several authors have used this method and have reported results that are in general agreement. Thus, according to Tarr, Oppenheimer, and Sager,²² the normal circulation time varies between 10 and 16 seconds. When congestion is present, either in the lungs, the vena cava area, or both, the circulation time is considerably prolonged, as has been clearly established by many authors during recent years. Congestion increases the circulation time to as much as 60 seconds or more.

Since 1933 we have measured the circulation time at the Seraphim Hospital and the Sabbatsberg Hospital in a considerable number of cases of heart disease. With regard to measurements of the circulation time alone, we have had, on the whole, the same experiences as other authors, but we have compared these measurements with the results of other examinations, particularly heart volume and venous pressure. It has been proved, as I shall show, that factors other than congestion, i.e., increased venous pressure, affect the circulation time.

During recent years we have directed our attention not only to the time that elapses from the time of injection until the bitter taste is perceived, but also to the patient's taste sensation. Thus, in several cases we have been able to fix the time of both maximal taste sensations and cessation of sensation, which normally occurs, at the latest, about 30 seconds after the injection.

We have followed several patients with cardiac insufficiency with repeated measurements during their return to compensation, as in the following case:

The patient was 55 years of age, and had hypertension and congestive heart failure. At the first examination the patient had anasarca, a heart volume of 2,100 c.c., and a venous pressure of 24 cm. Measurement of the circulation time: the first perception of taste was much delayed, i.e., 40 seconds, and the bitter taste did not disappear until after 70 seconds. Somewhat over three weeks later the congestion had diminished; the body weight had decreased by 5 kg.; the venous pressure had decreased to about half, i.e., 13 cm.; the time interval for the first taste sensation was considerably shortened, i.e., 18 seconds; and the duration was certainly shorter, i.e., 55 seconds, but nevertheless was considerably longer than normal. A month later, when the congestion and edema had disappeared, and the patient had lost 17 kg. in weight, and the venous pressure was only 6 cm. Circulation time: the first taste perception occurred after 20 seconds, was maximum at 30 seconds, and ceased at 40 seconds. The heart volume had decreased to 1,800 c.c., but the heart was still considerably enlarged.

The duration of the taste sensation was still prolonged, a fact to which, in my opinion, the greatest attention should be given. The signifi-

cance of the fact that, with an enlarged heart and no congestion, the circulation time is prolonged as regards both the first taste sensation and, above all, its duration, probably is that the enlarged heart is dilated and contains a considerable amount of residual blood. When the heart contains a large amount of residual blood, it must take a considerably longer time for the heart to empty its blood, including the decholin, than for a heart of normal size with a small amount of residual blood. As examples of prolonged circulation time—measured with decholin—and, above all, prolonged duration of the taste sensation when the heart is dilated and there are no signs of congestion, the following three cases are presented.

CASE 1.—G. R., a fitter, aged 62 years, had coronary sclerosis and hypertension, and had been short of breath on exertion for several years. His general condition was good. The sedimentation rate was 3 mm. in one hour. The urine was normal. The patient had no fever.

Physical examination showed no symptoms of cardiac insufficiency at rest. The blood pressure was 170/110. There were no cardiac murmurs. The patient had auricular fibrillation and a venous pressure of 8 cm. Circulation time: The first taste sensation occurred at 35 seconds, and taste perception ceased at 55 seconds.

Roentgenologic examination showed that the heart measured 17.5 in length, 13 in breadth, and had a sagittal diameter of 15 cm. The volume was 1,430 c.c., i.e., 700 c.c. per m² of body surface. The heart was generally enlarged, with some preponderance of the left ventricle. There was no congestion in the lungs. The cardiac pulsations were rather small and irregular.

The electrocardiogram showed auricular fibrillation, with a ventricular rate of 60 per minute. QRS measured 0.09 seconds. T₁ was positive, T₂, positive, and T₃, isoelectric. The S-T interval was slightly depressed in Leads I and II. The ventricular complexes were slightly notched in all leads. Diagnosis: Auricular fibrillation and partial bundle branch block.

CASE 2.—The patient was a 19-year-old schoolboy with congenital heart disease, i.e., isthmus stenosis with an enormous heart; the volume was 1,800 c.c., i.e., 930 c.c. per m² of body surface. There was no congestion anywhere. His venous pressure was 9 cm. At that time he still had a good reserve of strength, and performed even the severest functional test without difficulty. He played football without becoming breathless. Circulation time: first taste sensation at 20 seconds, maximum at 40 seconds, and cessation of taste sensation after 60 seconds. This case, in which congestion was entirely absent, was an excellent example of the fact that prolongation of the circulation time is determined by the degree of cardiac dilatation, i.e., by the amount of residual blood.

CASE 3.—The patient was a 45-year-old lift attendant who, for twenty-seven years, had had rheumatic mitral disease. Beginning in 1924, he had been a patient on many occasions at a number of hospitals in Stockholm, including the Sabbatsberg Hospital in 1940. After 1933 the heart volume increased enormously. On his admission to the Sabbatsberg Hospital, in 1940, remarkably enough there was no edema.

His general condition was fair. He had no fever. The sedimentation rate was 26 mm. in one hour. Physical examination showed no edema, but somewhat pronounced cyanosis of the face which increased on exertion. The liver was palpable two fingerbreadths below the costal arch (cardiac cirrhosis?). The blood pressure was 140/80, the vital capacity, 2,530, and the calculated vital capacity, 3,850.

The circulation time could not be measured with 5 c.c. of a 20 per cent decholin solution because the patient did not perceive any bitter taste. With 10 c.c. of a 20 per cent decholin solution, the first taste sensation was felt after 40 seconds. The taste sensation disappeared after 65 seconds.

Pronounced pulsations were visible over the precordia. The heaving apical impulse covered four fingerbreadths in the fourth intercostal space. Accentuated diastolic thrills were present over the lower left part of the thorax. Over the whole heart there was a long-drawn-out systolic murmur, with maximum intensity at the apex. At the apex, also, there was a long-drawn-out, rolling diastolic murmur. To the left of sternum a fairly long, rushing diastolic murmur was heard.

Roentgenologic examination showed that the heart was enormously enlarged, with pronounced pulsations all over. The total heart volume was 3,450 c.c., i.e., 1,740 c.c. per m² of body surface. There was moderately pronounced congestion of the lungs.

The electrocardiogram showed auricular fibrillation, with a ventricular rate of 90. T₁ was negative, and T₂ and T₃ were positive. QRS measured 0.09 seconds. The ventricular complexes were notched in all leads. Diagnosis: Auricular fibrillation, partial bundle branch block, and coronary insufficiency.

This case was remarkable in several respects. In the first place, I had never before seen such a large heart. Probably all the chambers of the heart were considerably dilated. Both the left and right auricles contributed very considerably to the enlargement, but it is extremely probable that, to a certain extent, the ventricles also participated. In the second place, the patient did not perceive any bitter taste with the ordinary amount of decholin, namely, 5 c.c., which every normal person and cardiac patient reacts to promptly. (It is naturally not ideal to use decholin as a test substance because the result depends on the sensation of taste.) In this case the explanation probably is that the large amount of residual blood diluted the decholin so much that no bitter taste was perceived. Not until twice the usual amount was given could the circulation time be measured, and then it was clearly prolonged; above all, the taste sensation was very protracted.

Study of these three cases of considerable enlargement of the heart, in which there were no insufficiency symptoms during rest (the venous pressure was practically normal, and there was no pulmonary stasis) shows clearly that the circulation time is determined not only by the degree of insufficiency and congestion, but also—and to a considerable extent—by the magnitude of the dilatation of the heart and, accordingly, the amount of residual blood, a circumstance to which attention has not been paid previously. It is not impossible, perhaps, in cases in which congestion is absent, to arrive at a conception of the degree of dilatation and the magnitude of the residual blood by means of measurements of the circulation time. An improved method for this purpose is being worked out, and experiments will be made to ascertain approximately the magnitude of the residual blood.

SUMMARY

The question whether the heart empties itself completely during systole has long been the subject of discussion. Everything indicates that

such is not the case, either under physiologic or—still less—under pathologic conditions.

Concerning the amount of blood which remains in the heart after systole, the so-called residual blood, extensive investigations have been made at the Seraphim Hospital and the Sabbatsberg Hospital. These investigations comprise (1) roentgenologic heart volume estimations under both physiologic and pathologic conditions, (2) post-mortem roentgenologic volume estimations, (3) post-mortem estimations of the heart volume by the displacement method, and (4) measurements of the capacity of the cavities. By this means, and with the help of circulation time measurements on patients with congestive heart failure and other patients with dilatation of the heart, but no failure, the amount of residual blood during life has been calculated approximately.

These investigations have shown:

(1) That, under both physiologic and pathologic conditions, the roentgenologic heart volume is subject to considerable changes which are due to variations in the amount of residual blood.

(2) That, with the help of ante- and post-mortem roentgenologic heart volume estimations, displacement estimations of heart volume, and measurement of the capacity of the cavities, it is possible to calculate approximately the residual blood during life. In certain cases the amount of residual blood during life may be quite large.

(3) That prolongation of the circulation time is not only an expression of congestive failure and retarded circulation—as has been generally considered—but is also, and largely, an indication of the amount of residual blood.

A method is being worked out for measuring the residual blood in vivo.

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RESTING PERIPHERAL BLOOD FLOW IN THE ANEMIC STATE

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IT IS well known that patients with anemia, even of a severe degree, show very few signs of cardiac distress when at rest. Since the function of oxygen transport is affected by anemia, it would be expected that certain cardiovascular adjustments must take place in order to maintain an adequate supply of oxygen to the tissues. In this connection, Morawitz and Röhmer¹ found that venous blood from resting patients with anemia had an oxygen saturation of only 15 to 50 per cent, as contrasted with 60 to 75 per cent in normal blood; this suggested that a greater than normal dissociation of oxygen from the hemoglobin takes place under these circumstances. Further, a number of investigators have noted a moderate augmentation of cardiac output²⁻⁴ and a reduced arm-to-tongue circulation time;^{5, 7} these observations constitute indirect evidence for the view that there is also an increased rate of blood flow in anemia. In contrast, Stewart,⁸ using the calorimeter, found a diminished circulation in the hand in this state, and Fahr and Ronzone³ noted many contracted cutaneous capillaries in the fingertips. According to the latter investigators, part of the oxygen supply to the tissues may be obtained by shifting of blood from the skin to other areas, where the metabolism is more active.

Since no adequate quantitative study of the peripheral circulation in human subjects with anemia has been reported, it was thought worth while to apply the venous occlusion plethysmographic method to this problem.

METHOD

Eleven anemic patients with no complicating factors, such as organic heart disease, were studied. The type and cause of the anemia and the degree of deficiency in the erythrocyte count and hemoglobin content differed in the various subjects. Only 2 were less than 50 years of age, and 7 were above 60. Blood flow measurements, in c.c. per minute per 100 c.c. of limb volume, were generally made simultaneously upon the two upper extremities; the technique employed was identical in all respects with that previously reported.⁹ The temperature of the water in the plethysmograph was maintained at 32° C., and the room temperature varied between 25° and 27° C. Fifteen to 20 readings were made after the patient had become accommodated to the environment and all psychic stimuli had been minimized. The pulse rate and blood pressure were ascertained in each experimental period.

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RESULTS

The results obtained were compared with those from a series of 25 normal persons of approximately the same age. The average control blood flow for the forearm was found to be 1.6 c.c. per minute per 100 c.c. of limb volume ($\sigma - 0.3$),* whereas that for the hand was 8.1 c.c. ($\sigma - 3.5$). Table I reveals that the forearm blood flow in 7 of the subjects with anemia was definitely increased; in 1 the readings fell within the higher range of the normal group; in 2 they were the same as the average of the controls; and, in 1 (L. Y.), the flow was below normal. The small flow in the case of subject L. Y. may be explained by the fact that he had been bedridden for many months. Patients M. S., C. B., and P. I. were examined on two occasions, and the readings recorded in Table I are the average of the different measurements. The average rate of forearm blood flow for the whole group of anemic patients was 2.5 c.c. per minute per 100 c.c. of limb volume, as compared with 1.6 c.c. for the normal subjects.

TABLE I
RATE OF RESTING BLOOD FLOW IN ANEMIC PATIENTS

SUBJECT	AGE	BLOOD FLOW IN C.C. PER MIN. PER 100 C.C. LIMB VOL.		B.P.	PULSE RATE	HGB. (GM.)	R.B.C.	REMARKS
		HAND	FORE- ARM					
M. S.	44	9.5	3.9	120/70		7.4	2.8 M.	Secondary anemia
L. Y.	74		0.8	106/50	72	8.4	2.8 M.	Debilitated
C. K.	68	3.3	1.7	120/74	84	7.25	2.23 M.	Acute bleeding; thrombocytes, 127,000
C. B.	59	6.2	2.0	96/56			2.9 M.	Bleeding peptic ulcer.
A. L.	75	4.1	2.2	148/80		7.4	3.5 M.	
H. C.	24	5.5	3.8	110/60	92	9.6	3.0 M.	Banti's disease
A. B.	54	7.3	2.2	146/88	88	7.7	4.4 M.	Ga. of stomach
R. E.	72	11.1	3.3	200/60	105	6.8	4.5 M.	
A. K.	65	5.7	1.5	160/82	82	9.4	2.8 M.	Nutritional anemia ?
P. I.	63	3.8	2.3	158/88	72	7.6	2.8 M.	Pernicious anemia
H. F.	76		3.8	114/54	87	5.1	1.8 M.	Hemolytic anemia

As regards the circulation in the hand, the general trend appeared to be towards a somewhat decreased or low normal blood flow. Three patients had readings that were significantly less than normal, whereas those of the remaining six fell within the control range. The average for the group, as a whole, was 6.3 c.c. per minute per 100 c.c. of limb volume, as compared with 8.1 c.c. ($\sigma - 3.5$) for the normal persons. No distinct relationship appeared to exist between the degree of anemia and the rate of blood flow through either the hand or the forearm.

DISCUSSION

As previously stated, there is some evidence for the view that a greater than normal utilization of the arterial oxygen takes place in anemia.

*Standard deviation.

With respect to this hypothesis, Liljestrand and Stenström⁴ have suggested that the ability of the tissues to obtain oxygen under the reduced tension that is present in the anemic state depends upon the opening up of new capillaries, with a consequent increase in the diffusion surface. However, there is a definite limit to the quantity of oxygen that can be made available through this means, for, the lower the hemoglobin content, the smaller will be the absolute amount of the gas which can be given off from each 100 c.c. of blood.

Increase in the cardiac output²⁻⁶ and the tendency toward an augmented peripheral circulation through the forearm, as observed in the present study, constitute evidence for the view that another compensatory mechanism operates in the anemic state, namely, an increase in the rate of blood flow through the tissues. The relative decrease in the circulation in the hand cannot be interpreted as suggesting a shunting of blood from the cutaneous vessels to other vascular beds, for the blood flow in the hand is normally affected by many types of vasoconstricting stimuli.¹⁰

It would appear, therefore, that, in the anemic state, a normal oxygen supply to the tissues is maintained by both a moderate increase in the rate of blood flow and a greater utilization of the oxygen in the arterial blood. However, since these are the mechanisms called into play in the normal subject during muscular work, it is obvious that the cardiovascular system in the resting anemic subject is already geared to the equivalent of a higher level of effort, and hence even slight physical exertion may heavily strain its capacity.

SUMMARY

By means of the venous occlusion plethysmographic method, the peripheral circulation was investigated in a series of eleven patients with anemia of various types.

A moderate increase in blood flow was observed in the forearm, but in the hand the readings were, for the most part, within the lower range of normal or somewhat decreased.

The observations on the forearm constitute direct confirmation of the view that one of the compensatory mechanisms elicited in the anemic state is an augmented circulation through the tissues.

The authors wish to express their appreciation to Mrs. William Littleford for valuable technical assistance.

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THE RANGE OF THE NORMAL HEART IN ATHLETES

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DISEASES and defects of the cardiovascular system seem to be the principal causes in total disqualifications for any military service.'"¹

In our war for survival, the serious analysis of all possible factors contributing to total rejection for active service and possible procedures for their correction seem fundamentally essential. Had I not held the deep conviction that my seemingly academic subject has very practical relationships to our present and future military efforts and general manpower conservation, I would not have prepared this paper.

Nationally speaking, many athletes who should furnish some of our best general military, officer, and aviation pilot material are being legitimately rejected from service for cardiac, as well as for many other medical and surgical, conditions. Broad participation in competitive athletics and strenuous recreative sport and physical education for practically all ages and both sexes is a definite and characteristic part of the life of our American democracy, but there is still a great deal to be learned concerning the cardiac effects of athletics.

Constant consideration of the many and varied medical aspects of exercise is appropriate, in order that its effects may be continuously constructive. Some of us have made investigations of certain parts of the field, and much information has been acquired, but our knowledge is still incomplete. The Levine-Sosman group's continuing study of marathon runners and the Harvard Grant study seem particularly promising.

The essential background of the general athletic cardiac question is found in the following selected opinions. White says, "Physical work and exercise do not cause heart disease, though they may precipitate or aggravate symptoms and signs of heart disease already present and may temporarily exhaust the cardiovascular reserve even in a healthy individual."² Lewis states, "Burdens imposed by physiological acts upon the normal heart, however heavy these burdens, may be said *never* to injure heart fibers, *never* to produce injurious dilatations, and *never* to exhaust the heart's reserve."³ Dublin, whose work on the longevity of college athletes is classic, states that "Indulgence in athletics may in a good many instances have deleterious effects on the heart, especially if careful selection and supervision of athletes by trained men is not

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available."⁴ Cole states, "Our business is to look for cardiac defects and protect the defective heart. For the heart that has proven itself healthy we have no concern."⁵ But what is a "healthy," so-called "normal" heart from the athletic standpoint?

PRESENT STUDY

The writer has made an investigation which was started to obtain evidence concerning the following postulates:

1. "Athletic heart," in the sense of a permanently enlarged, clinically inferior heart, does not exist in the absence of etiologic factors which are scientifically accepted as the cause of actual or potential cardiac disease.

2. *Under present conditions of American athletics*, many inferior or potentially inferior hearts of competing athletes may have their inferiority factor increased by athletic competition or by any degree of exercise which is too heavy for a particular person.

3. Certain so-called normal hearts may show relatively minor, transitory, physiologic size changes which have little, if any, practical clinical significance.

The present study gives objective data concerning the supposedly normal hearts of American athletes as they present themselves for health examinations.

The evidence submitted at this time is based primarily on a thirteen-year study of the history and cardiac size of 233 male American athletes whose ages ranged from 16 to 80 years; they were selected from 3,000 cases. The cases are well distributed up to the age of 50. The classification of "athlete" is based on my own judgment, after forty years of contact with the field in varying capacities.

TABLE I
AGE RANGE OF AMERICAN MALE ATHLETES

AGES	NUMBER IN GROUP	PER CENT
16-24	59	23.41
25-29	61	24.20
30-39	74	29.36
40-49	34	13.49
50-59	19	7.53
60-69	3	1.19
70-79	1	0.39
Over 79	1	0.39

METHODS USED

Orthodiagrams were made of the anteroposterior heart shadow in diastole during quiet respiration, in the upright position (as well as many "obliques" in questionable cases). The cardiac area was measured with a planimeter, after completion of the upper and lower borders. Area and diameter were ascertained, and percentages of the deviations from normal were computed according to the Hodges and Eyster postulated normal cardiac areas and diameters, based on age, height, and

weight, using the Kurtz nomogram, and checked with the cardiac slide rule. The size was also ascertained by the cardiothoracic ratio method of Danzer, but this was considered less accurate.

The study is secondarily a clear illustration of the great variation in the estimate of heart size by these methods.

Electrocardiograms, functional tests, and the essentials of physical examination were obtained in a large percentage, but not in all, of the cases.

In this study, plus 10 per cent is considered the upper limit of normal area; 0 per cent is the average normal of both area and diameter figures. The area method of judgment as to size was used primarily.

TABLE II
CARDIAC SIZE OF 233 AMERICAN MALE ATHLETES

	AGE	% DEVIATION AREA +	% DEVIATION AREA -	% DEVIATION DIAMETER +	% DEVIATION DIAMETER -	% C.T.R.
Means	32.6	17.75	8.01	9.5	6.51	48.89
Extremes						
a) Max.	80	65.5	27.8	41.2	28.47	66.6
b) Min.	16	0	0.8	0	0	38.7
Cases		177	77	161	93	254
Algebraic Mean of % Deviation		Areas 9.94+		Diameters 3.63+		

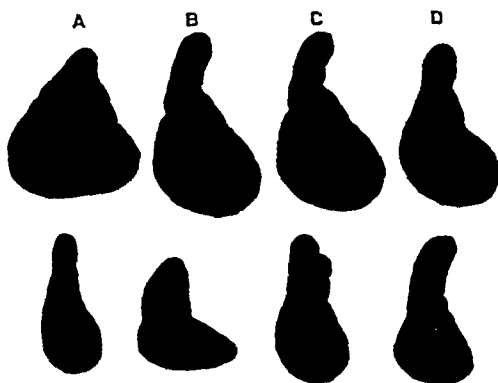


Fig. 1.—Maximum and minimum heart areas in study groups. A, 3000 athletes; B, 233 persons. American male athletes; statistics in Table II; C, "organic" or "marked inferiority factor" hearts; increased injury by 36 athletes. See statistics in Table III.

ARE ATHLETES' HEARTS NORMALLY ENLARGED?

The popular belief of laymen and many physicians is that the heart, like any other muscle, enlarges under conditions of work or exercise. *Athletes' hearts are not all enlarged; some are enlarged, some are normal, and some are small.* In my series the cardiac areas ranged from plus 65.5 per cent to minus 27.8 per cent. The algebraic mean of all

areas from 233 persons and 254 tracings was plus 9.94. One hundred thirteen of 233 hearts were absolutely enlarged, that is, larger than the *allowed normal* area range of 10 per cent above *average normal* (0 per cent). One hundred twenty were below this standard of normal size. Absolute enlargements exist, and would be called athletic hearts by some, but size increase may be explained by inheritance, disease, or deficiency factors before, during, or after active sport.

A few cases illustrating the present heart sizes of older athletes are presented in Fig. 2.

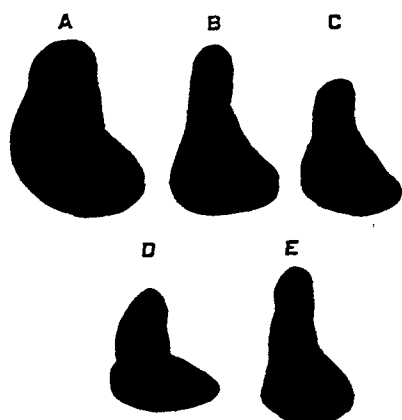


Fig. 2.—Athletes' geriatric aspects. Five cases illustrating present heart sizes of older athletes. (C.T.R. = Cardiothoracic ratio.) A, Aged 80 years, Ht. 73 inches, Wt. 206 pounds, area 49.6% plus, diameter 38.4 plus, C.T.R. 53.5%. B, Aged 56 years, Ht. 74 inches, Wt. 218 pounds, area 1.47% plus, diameter 6.61 minus, C.T.R. 46.6%. C, Aged 62 years, Ht. 66 inches, Wt. 174 pounds, area 11.92% minus, C.T.R. 54.3%. D, Aged 53 years, Ht. 68½ inches, Wt. 190 pounds, area 19.64 % minus, diameter 40.67 plus, C.T.R. 57.8%. E, Aged 55 years, Ht. 73½ inches, Wt. 179 pounds, area 27.8% minus, C.T.R. 42.8%.

A. Yale athlete. One of the earliest football and crew men, aged 80 years. Cardiac area 49.6 per cent plus deviation. This sportsman and golfer, forty years after college competition, gave a history of many potential heart disease factors, including diphtheria. Increased heart size is explainable as a result of disease plus sport factors. Although his heart was organically enlarged, his general constitutional strength made possible a long and useful life. Pneumonia was the cause of death.

B. One of Michigan's greatest Olympic track and football stars, thirty years after. Cardiac area showed a 1.47 per cent plus deviation.

C. Cornell and Pennsylvania athlete, aged 62 years, fine all-around athlete in college—baseball, football, track, sprinting. Practice of medicine and moderate recreative sports since. Excellent condition for age. Cardiac area showed 11.92 per cent minus deviation.

D. One of Colgate's greatest all-around athletes, Olympic track hurdle winner and All-American football player, thirty years after competition. Cardiac area showed a 19.64 per cent minus deviation.

E. Washington and Jefferson all-around athlete, aged 55 years. Cardiac area showed a 27.8 per cent minus deviation. This area was much below the average normal, in spite of the history of proved, early, organic rheumatic heart disease, with rheumatic fever three years before examination.

NORMAL CARDIAC VARIATIONS IN RELATION TO BODY HABITUS

The usual normal constitutional variations in heart shape are naturally also normal for athletes. The vertical cardiac position is less frequently seen than the oblique and lateral. An excellent illustration of this normal contrast is furnished by two Chicago University athletes twenty years after competition (Fig. 3). From personal knowledge, these were two of the best all-around athletes in the old days of Chicago's athletic superiority. They had approximately the same athletic experience, namely, football, basketball, baseball, and track, both in high school and college, approximately the same postgraduate exercise, and no recognizable potential or organic heart disease factors. There was much less than the usual degree of dental caries in both cases.

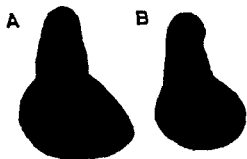


Fig. 3.

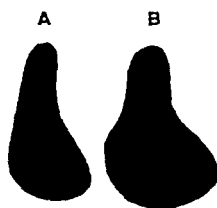


Fig. 4.

Fig. 3.—Normal body habitus and cardiac variations. *A*, Aged 42 years, Ht. 68 inches, Wt. 180 pounds, area 32.45% plus, diameter 23.86 plus, C.T.R. 59.2%. *B*, Aged 48 years, Ht. 73 inches, Wt. 180 pounds, area 12% minus, diameter 6.82 minus, C.T.R. 40.4%.

Fig. 4.—Twenty-year follow-up of two Wisconsin crewmen. *A*, Aged 37 years, Ht. 72 inches, Wt. 182 pounds, area 20.63% minus, diameter 10 minus, C.T.R. 48.1%. Normal heart. *B*, Aged 42 years, Ht. 74½ inches, Wt. 227 pounds, area 18.7% plus, diameter 12.5 plus, C.T.R. 52.7%. Deceased age 49. Lymphosarcoma.

Twenty years after competition, the heart area of the man of sthenic type showed a 32.45 per cent plus variation, whereas the area of the heart of the tall, coördinated, so-called true athletic type showed a 12 per cent minus variation. It is fair to say that the sthenic athlete had more natural energy. Both engaged in track sports and baseball in the spring, but the sthenic man had indulged in two-mile competition in a small quantitative degree, whereas the taller man had indulged in much less strenuous high jumping.

TWENTY-YEAR FOLLOW-UP STUDY OF TWO WISCONSIN CREW MEN

Two cases are presented (Fig. 4) as twenty-year "follow-ups"; these boys were in the Schumacher and Middleton⁸ series at Wisconsin in the years 1912 and 1913. Both boys were excluded from crew work at that time because of enlarged hearts. Twenty years after the first examination, the heart of the first man (Case 14) was not enlarged and showed no evidence of disease. It is entirely possible, of course, that the heart was enlarged at the earlier time, and returned to normal when the lad was taken away from intensive activity. The heart may have been saved a longer period of enlargement by restriction in exercise.

The heart of the second man (Case 15) was entirely different. Twenty

years after the first examination it was enlarged, and the electrocardiogram showed an abnormal degree of left axis deviation. The basal metabolic rate at the time of my examination, in 1933, was -24 per cent. This man has not indulged in active recreative sport in the degree that might have influenced his heart size since graduation. I believe that this heart inherited a tendency to abnormality. The myxedema heart syndrome is possible in this case. Other inferiority factors, outside of a slight chronic sinus condition, played no part. I believe that this heart was enlarged at the time of the Wisconsin examination, but that it was even then a "hypothyroid heart," possibly exaggerated by high school athletic experience. This is purely an opinion. I knew the physical and personal characteristics of these men at the time of the Middleton examination.

It may be of significance that the lymphoid disease tendencies in Case 12 of my series have been confirmed; this man recently died at the age of 48 years from lymphosarcoma. I cannot correlate any athletic factor with his early death.

It was not until 1927 that the English translation by an outstanding internist, Louis M. Warfield, of *Heart and Athletics*, by Felix Deutsch and Emil Kauf, gave real support to the previously questioned presentation of Schumacher and Middleton.⁸

"STRICTLY NORMAL" ATHLETES' HEARTS

Strictly speaking, a normal, healthy heart is one which shows no evidence of organic disease, congenital or acquired, no abnormal variation in size or shape under accepted standards, no evidence of deficiency or degenerative conditions, no abnormal variation in functional efficiency, and no history of any condition which is known to predispose to heart disease or to favor it.

The most amazing thing to me in my entire study was that, by these present-day standards, *only twenty-nine hearts in my entire group of 233 cases were "normal."* If we omit from our definition "no abnormal variation in size or shape under accepted standards," thirty-seven were normal.

I have classified these thirty-seven athletes, who have competed intensively in American sport and qualified under the above definition of "strictly normal," as normal. They have never had organic disease, or any disease included in the army and navy lists or in the criteria for cardiac diagnosis as potential heart disease factors, namely, scarlet fever, chorea, diphtheria, measles, rheumatic fever, tonsillitis, influenza, typhoid fever, syphilis, gonorrhea, tuberculosis, or chronic focal infection.^{6, 7} They are normal athletes, with absolutely normal function, so that athletics is postulated as the only possible influence on heart size. The evidence, that of their own histories, is limited in accuracy, as is all patient's testimony.

The range of normal of these hearts is shown in Table III. These

TABLE III

CARDIAC SIZE AMONG AMERICAN MALE ATHLETES; SPECIAL GROUP OF 37 CASES IN WHICH THERE WAS NO DISEASE (POSTULATED "NORMAL")

	AGE	% DEVIATION AREA +	% DEVIATION AREA -	% DEVIATION DIAMETER +	% DEVIATION DIAMETER -	% C.T.R.
Means	33.8	9.68	6.66	8.34	6.7	46.65
Extremes						
a) Max.	70	20.3	17.69	19.03	18.4	64.8
b) Min.	17	0.89	1.69	1.639	0	33.6
Cases		18	19	12	25	37
Algebraic Mean of % Deviations		Areas 1.29-		Diameters 1.82-		

CASE *	SIZE ORDER AREA	SIZE ORDER C.T.R. †	NAME	AGE	AREA % DEV. +	AREA % DEV. -	TRANS. DIAM. % DEV. +	TRANS. DIAM. % DEV. -	% C.T.R.
105	1	18	E. M.	26	20.3		8.53		45.7
45	2	7	R. E.	45	19.7		1.95		51.4
46	3	15	J. E.	31	17.93		1.561		47
71	4	6 (a)	W. H.	27	15.8		12.3		53
143 (b)	5	2	C. S.	32	15.26		12.98		56.4
130	6	5	C. P.	70	14.6		7.03		53.7
4	7	31	F. B.	29	14.5			14.4	33.6
143 (a)	8	3	C. S.	23	10.7		10.93		55.2

Hypothesized as Physiologic "Athletic" or "Work" Hearts

188	9	6 (b)	S. W.	41	9.92		8.83		53
106	10	10	S. M.	32	9.91		7.2		50
151	11	23	M. S.	27	8.41		2.46		43.4
41	12	1	J. D.	49	5.1		19.03		64.8
146	13	11	C. S.	35	4.34			7.1	49.4
97	14	20	J. G. L.	38	3.57		1.639		43.7
55	15	14	J. G.	28	1.612			6.72	47.1
49	16	19	R. H. E.	35	0.926		0.847		43.9
147	17	9	H. S. S.	43	0.918			0	50.4
59	18	4	E. G.	39	0.893			7.26	54.5
32	19	28	C. C. C.	40		0.826		7.87	40.8
168	20	17 (b)	B. C. T.	17	1.69			1.6	45.8
164	21	29 (b)	F. S.	25	2.43			4.23	40.2
117	22	13	C. S. O.	24	2.479			0	48.1
66	23	29 (a)	A. H.	43	2.52			18.4	40.2
19	24	8	H. D. S.	35	2.9			5.41	50.7
155	25	24 (b)	O. B. S.	35	2.9			9.93	42.5
166	26	12	H. S.	35	3.64			3.97	49.1
192	27	25	H. W.	32	6.03			6.35	42.1
54	28	24 (a)	G. F.	24	6.37			.573	42.5
141	29	17 (a)	D. R.	28	6.45			12.68	45.8
193	30	27	W. W.	32	6.96			10.5	41.1
139	31	16	R. R.	27	7.62			1.502	46.3
65	32	24	P. G.	26	8.7			8.94	43
125	33	30	D. P.	33	9.92			6.3	39.6
112	34	22 (b)	B. M.	33	9.92			13.62	43.5
131	35	26	M. P.	24	10.43			11.81	41.5
102	36	21	B. M.	40	17.69			7.9	43.6
31	37	22 (a)	E. C.	49	17.1			5.425	43.5

*Individual cases have numbers. Cases such as 143 are lettered (a) for first examination, and (b) for second examination, etc.

†Letters following numbers signify, for example, that Case 71 has sixth largest C. T. R., noted as 6 (a). Case 188 had the same C. T. R., is also sixth in C. T. R. size order, but is given order number 6 (b) to differentiate.

areas range from deviations of 20.3 per cent plus to 17.69 per cent minus. The algebraic mean area was 1.29 per cent plus, against a postulated upper limit of normal of 10 per cent plus. The algebraic mean diameter was 1.82 per cent minus.

Since no Wassermann reactions, vitamin B deficiency tests, or basal metabolism measurements were done, it is not claimed that this evidence is conclusive. Clinical inspection showed no evidence of hypothyroidism. Compared to some investigations of the subject in the past, from which many have generalized, this examination is relatively satisfactory because the vitamin B and metabolism deficiency influences on the size of the heart were not known twenty-five years ago, and their potential influence is still very incompletely considered.

Granting, for the moment, that the possible error of omission was not actual, *seven of the thirty-seven hearts which were postulated as normal were enlarged by athletic competition, and would qualify as true athletic or work hearts, or normal hearts physiologically enlarged by exercise.* These hearts were absolutely normal clinically and functionally. The eventual significance of their enlargement is unknown. According to my belief, they are normal for all practical purposes, and will permit a normal or greater than normal life expectancy.

DAMAGED HEARTS AND ATHLETICS

The second postulate is "under present conditions of American athletics *many* athletes with organic or inferior value or potentially inferior value hearts compete." The abnormalities of such hearts may be, and often are, increased by athletic competition or any excessive degree of exercise. What present-day conditions in American sports¹⁰⁻¹¹ are pertinent to our discussion?

Many athletes compete in American sports today who should not be allowed to do so, medically speaking, for the following reasons:

1. No pre-sport examination. This condition does not exist in the better colleges, but 28 per cent of 9,000 college freshmen testified to this situation in their high school and earlier experience.

2. Inadequate pre-sport history or examination, and omission, in many instances, of any medical opinion before return to sport after illness.

3. Lack of accepted medical standards for participation in various types of sports.

4. Personal neglect of the doctor's order because there is a tremendous psychologic, physical, and social satisfaction in sports.

5. Desire of parents who want the thrill and secondary advantage of their sons' athletic prowess.

6. Public opinion and pressure on athlete and doctor to allow good athletes to compete.

7. Occasional political, instead of educational, sports and recreational administration.

8. Great public recreational systems in which players are allowed to compete intensively without medical examination of any kind.

9. The prevalence of informal "sandlot" type competition, with no formal medical "participation control."

10. The national tendency to promote team competition for "grade schoolers" without adequate medical guidance.

11. Sports articles in popular magazines which occasionally promote the public acceptance of "half truths" concerning the medical effects of sport.

Many athletes are denied participation in American sports who should be allowed to compete for the following reasons:

1. The medical viewpoint of what constitutes the proper medical standards for participation in various sports varies a great deal.

2. Many boys are excused from sport because of a "murmur," although certain leading cardiologists and other physicians allow persons with small degrees of chronic valvular involvement certain degrees of participation.

3. Cases need individualization in the light of relative evaluation of social, economic, and psychologic values, as balanced against possible medical injury through participation.

The lay viewpoint of this whole question of the effect of athletics on the heart is influenced by newspaper reports such as the following:

BOY HITS HOMER, RUNS BASES, DIES

Bellefontaine, O., May 7.—(A.P.)—J. E. D., 13, hit a home run in a school baseball game today, circled the bases, and fell dead. Physicians blamed heart disease.

SICK RUNNER IS VICTORIOUS

Boston, April 20 (A.P.)—Students of long-distance running today were asking themselves just what J. S., the National A.A.U. marathon champion, would have done to the Boston A.A.'s Blue-Ribbon field if he really had felt fit.

The 27-year-old Medford milkman, so weakened by a recent influenza attack that he did not believe he could go more than 15 miles, yesterday clipped one minute, thirty-seven and two-fifths seconds off the famed Hopkinton-Boston course record, while outdistancing the closest of his 113 rivals by more than a quarter-mile. His time for the 26-mile, 385-yard classic was two hours, twenty-six minutes, fifty-one and one-fifth seconds.

It is logical to assume that a moderately damaged heart might be stronger than normal at some time before decompensation.

The volume, *Nomenclature and Criteria for the Diagnosis of Diseases of the Heart*, carries this pertinent example under Therapeutic Classification: "The functional capacity of the patient does not always determine the amount of activity which is permitted. For example, a child with active rheumatic carditis may not experience discomfort in playing baseball yet the physician knows that rest in bed is imperative."¹⁹ Many athletes compete under this principle with less extreme medical conditions. These athletes are normal from the lay standpoint, regardless of the possible eventual bad effects of competition.

The capacity of some diseased or inferior hearts to take punishment in sport or work is tremendous. That is the reason so many athletes are considered normal when careful medical examination or post-mortem study after suicide or accident reveals organic changes in the heart valves, muscle, or pericardium before the heart had lost enough of its functional power to be noticeable to the public, athlete, coach, or trainer.

Data on the diagnosis of generalized enlargement of the heart in athletes (athlete's heart), without analysis as to cause, are given in Table IV.

TABLE IV

CARDIAC SIZE AMONG AMERICAN MALE ATHLETES; SPECIAL GROUP OF ABNORMAL HEARTS (DISEASE PRESUMABLY RELATED TO ATHLETICS)

		% DEVIATION AREA +	% DEVIATION AREA -	% DEVIATION DIAMETER +	% DEVIATION DIAMETER -	% C.T.R.
Means	24.2	28	1 case only	15.08	7.24	51.48
Extremes						
a) Max.	41	65.5	9.26	41.2	12.3	66.4
b) Min.	16	4.1	9.26	0.782	0.826	40
Cases	29	28	1	26	3	29
Algebraic Mean of % Deviations		Areas 26.73+		Diameters 12.77+		

CASE	SIZE ORDER AREA	SIZE ORDER C.T.R.	NAME	AGE	AREA % DEV. +	AREA % DEV. -	TRANS. DIAM. % DEV. +	TRANS. DIAM. % DEV. -	% C.T.R.
230 (a)	1	10	R. W. M.	32	65.5		36.2		55.4
219	2	2	V. W. E.	19	54.3		41.2		66.4
230 (b)	3	4	R. W. M.	34	52.6		33.62		59.1
221	4	11 (a)	G. E.	21	48.6		22.5		53.3
224 (b)	5 (a)	5	M. F.	24	41.1		30.0		56.2
225	5 (b)	3	H. F.	21	41.1		16.54		61.5
220	6	12	M. E.	29	40.7		26.8		55.5
238	7	13	H. M. S.	23	40.5		7.58		50.3
235	8	11 (b)	H. S.	23	37.6		5.35		53.3
232	9	8	F. P.	37	36.2		26.6		56.0
231	10	18	C. P.	17	33.3		19.67		47.9
215 (c)	11	14	H. B.	16	31.2		11.88		51.1
227	12	19 (a)	H. P. H.	28	30.1		13.56		47.8
224 (a)	13	6	M. F.	22	30		23.6		58.2
218	14	23	C. R. C.	34	28.3		11.4		45.0
223	15	19 (b)	R. F.	20	25.9		9.6		47.8
233	16	16	W. W. R.	23	25.4		8.89		51.5
237	17	20 (a)	C. S.	23	24.56		6.4		47.6
239	18	21	R. S.	28	24.35		4.03		47.2
236	19	24	B. S.	18	21.36		1.82		43.5
228	20	22	H. K.	23	20.83		9.09		45.5
226	21	20 (b)	H. C. G.	23	14.9		3.96		47.6
215 (b)	22	17	H. B.	16	12.84		0.848		48.5
222	23	20 (c)	P. A. E.	23	10.09			0.826	47.6
217	24	1	R. C.	41	8.26		14.3		66.6
215 (a)	25	15	H. B.	16	8.2		5.9		51.0
216	26	26	L. C.	21	6.96			12.3	39.0
229	27	9	H. J. K.	18	6.67		0.782		52.8
234	28	25	C. R.	29		9.26		8.62	40.0

For explanation of (a), (b), (c) see footnotes, Table III.

This is the group in which active participation in sport has been preceded, accompanied, or followed by significant organic or potential heart disease. The maximum deviation in the frontal heart area of this group is 66 per cent plus, and the minimum is 9 per cent minus. The algebraic mean area is 26.73 per cent plus, and the diameter, 12.77 per cent plus.

Every person in this series was *normal from the viewpoint of the trainer or layman*. All of these boys and men are getting along perfectly well and successfully indulging in various degrees of recreative and competitive physical activity. The interpretation as "normal" of all who can successfully engage in practical competition without dropping dead is widely accepted. *This makes for much misunderstanding between laymen and those physicians who try to practice preventive medicine.* Attempts to avoid the common cardiac neuroses must naturally also be a part of preventive medicine.

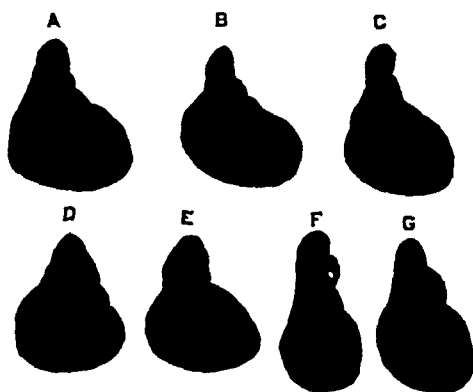


Fig. 5.—Radically organic heart disease in competing athletes. Athletic exaggeration of condition postulated. A, Aged 37 years, Ht. 5 feet 6½ inches, Wt. 160 pounds, area 84.26% plus, diameter 39.68 plus, C.T.R. 66.9%. B, Aged 18 years, Ht. 5 feet 11 inches, Wt. 183 pounds, area 50% plus, diameter 33 plus, C.T.R. 62%. C, Aged 21 years, Ht. 5 feet 7½ inches, Wt. 142 pounds, area 65.42% plus, diameter 32.45 plus, C.T.R. 61.5%. D, Aged 17 years, Ht. 67½ inches, Wt. 114 pounds, area 57.28% plus, diameter 41.12 plus, C.T.R. 66.7%. E, F, G, Other cases.

ILLUSTRATIVE CASES

A. A 37-year-old man with chronic rheumatic heart disease, area enlargement of 85 per cent plus, and auricular fibrillation, played thirty-six holes of golf a day on a hilly course before I saw him. He later bowled as many as fifty match games daily. I saw him two years after his first visit. His hypertrophy was reduced to 56 per cent plus after marked reduction of exercise (and happier marriage). His auricular fibrillation persisted (no deficit), and he was about to bowl three events in the American Bowling Congress at the time. In the lay mind, he was entirely normal for such activity.

B. Very marked aortic regurgitation, with marked left ventricular enlargement, was found in the case of a surprised boy, immediately after "all city" high school all-sports competition in Ohio's largest city school system.

C. A college freshman with chronic rheumatic mitral disease, a cardiac area showing a 65 per cent plus enlargement, and normal function was "normal" for all high school sport and freshman football before his disease was discovered. He played in high school and started to play in college with the consent of his family physician and of his father.

D. A boy with active rheumatic carditis and mitral disease was picked up by chance while competing in intramural athletics.

An exceptionally strong, well-endowed man, because of his high natural endowment, may perform normally in strenuous activity in spite of organic disease or handicap. A normal performance for the athlete with relatively great resistance and endowment is vastly different from that of the normal heart of an average man for average activity.

Degree of infection depends on the number and virulence of organisms and body resistance. Normal heart function and what a person may do with immediate or eventual safety depend on the degree of heart disease as related to constitutional strength, habitus, and endocrine and general organic make-up. In the cases noted above, and in many others which could be cited, the heart was normal for the degree of competition indulged in only in the light of the above formula. They were not cases of healthy hearts.

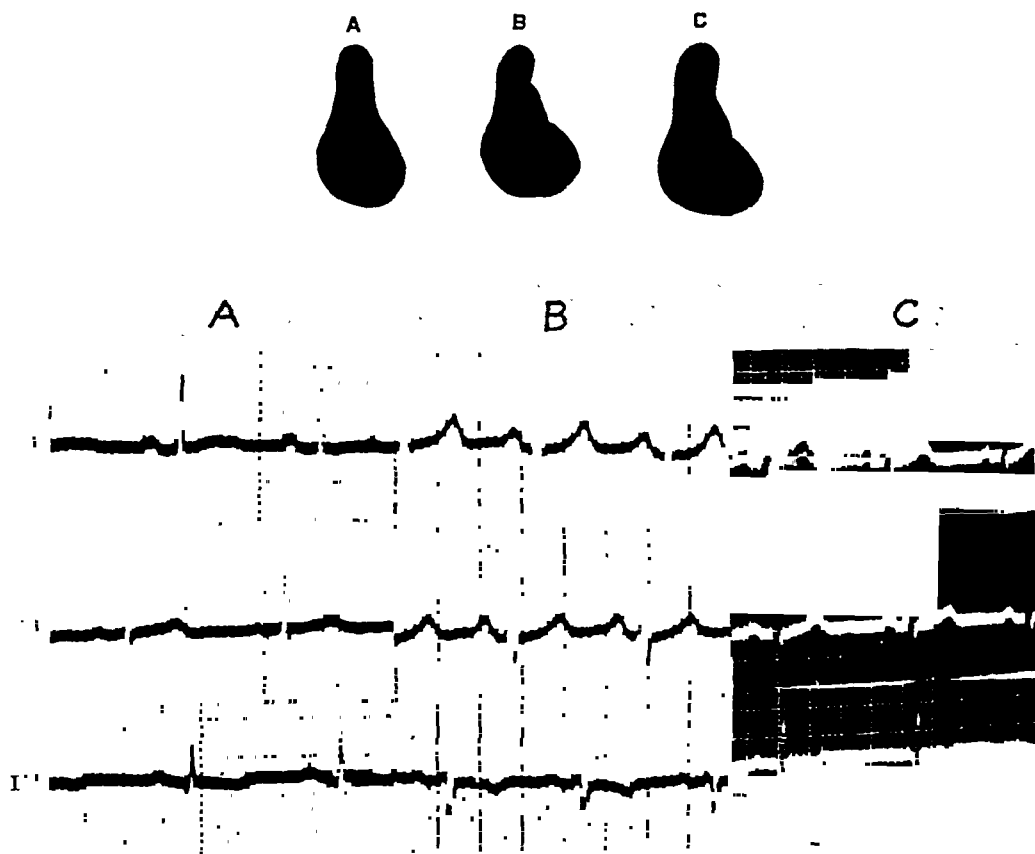


Fig. 6.—Heart size changes postulated as physiologic. Olympic sprint champion. *A*, Aged 22 years, Ht. 71½ inches, Wt. 152 pounds, area 15.38% minus, diameter 5.04 minus, C.T.R. 47%. *B*, Aged 24 years, Ht. 71½ inches, Wt. 162 pounds, area 9.3% minus, diameter 0.8 minus, C.T.R. 49.1%. *C*, Aged 26 years, Ht. 71½ inches, Wt. 157 pounds, area 3.3% minus, diameter 13.11, C.T.R. 50.9%. Note left axis deviation in electrocardiogram, with return to normal in electrocardiogram *C*.

The writer originally suggested the appropriateness of using a clinical diagnostic phrase to describe such hearts as Cases 1, 2, and 4, as "rheu-

matic athletic," etc.,¹² including athletics as a contributing etiologic factor. Case 1 (upper left) and other cases in which competition in sports was thought to have increased the already existing abnormality are shown in Fig. 4.

PHYSIOLOGIC CHANGES IN THE SIZE OF THE HEART

The third phase of our thesis is that certain so-called normal hearts may show relatively minor, transitory, physiologic changes in size which have little or no practical significance.

The heart of an Olympic champion sprinter, under especially strenuous, pre-tryout, meet-training conditions, made necessary by injury, changed in area and contour and showed transitory left axis deviation in the electrocardiogram. Two years after discontinuing Olympic training, his heart showed an additional, slight increase in size, with only recreative sport and running, possibly because of the pre-Olympic strain. It was still not absolutely enlarged (see Fig. 6).

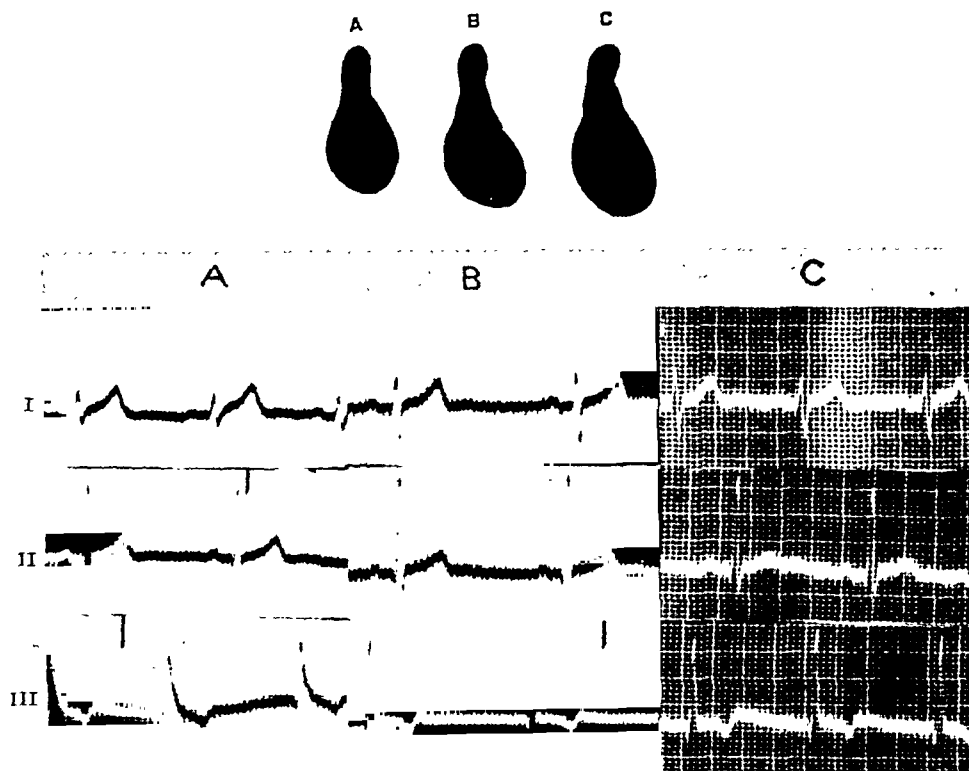


Fig. 7.—Heart size changes postulated as physiologic. High school tennis, basketball star. A, Aged 15 years, Ht. 75 inches, Wt. 150 pounds, area 20% minus, diameter 9.48 minus, C.T.R. 39.6%. B, Aged 16 years, Ht. 75 inches, Wt. 150 pounds, area 1.6% minus, diameter 5.17 minus, C.T.R. 40.5%. C, Aged 17 years, Ht. 76 inches, Wt. 170 pounds, area 3.7% plus, diameter 6.5, C.T.R. 42.6%.

The heart of a high school basketball star was examined over a period of three years; it gradually increased in size, but was still not absolutely enlarged. He is now a star at Notre Dame (see Fig. 7).

PATHOLOGIC CHANGES IN THE SIZE OF THE HEART

A high school coach brought in his star basketball player, who had been, in my opinion correctly, ruled out of competition by a local physician. The boy insisted that he would play anyway on an independent team, and therefore was given permission to play part time with the high school. He was seen three months later at the start of the basketball season. Much to my surprise, the coach had decided to "build the boy up and condition him" on his own responsibility. He had sent the player through strenuous practices, although allowing him participation in only alternating quarters, as agreed to previously. The boy's cardiac area had increased from 12.84 per cent plus to 31.2 per cent plus in three months, as illustrated by Fig. 8.

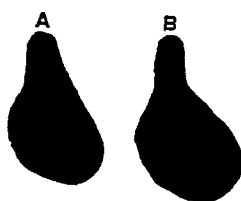


Fig. 8.—Heart size changes postulated as pathologic. A. Aged 16 years, Ht. 68 inches, Wt. 145 pounds, area 12.84% plus, C.T.R. 48.5%. B, Same. Three months later. Area 31.2% plus, C.T.R. 51.1%.

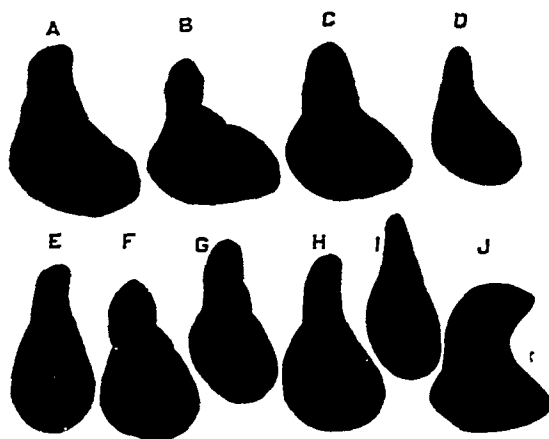


Fig. 9.—"Athletic hearts" as diagnosed by various physicians.

HEART	AGE	HT. INCHES	WT. POUNDS	AREA %	DIAMETER %	% C.T.R.
A	48	73	225	30.3 plus	21.35 plus	59.0
B	26	71½	210	25.2 plus	17.6 plus	63.01
C	52	68	190	21.55 plus	13.04 plus	59
D	17	62	128½	12.84 plus	0	48.5
E	22	73	160	9.83 plus	5.74 minus	43.4
F	23	73½	164	6.45 plus	4.07 minus	44.9
G	22	68½	142	1.83 plus	4.27 minus	42.1
H	38	71	169	0.84 minus	0	46.0
I	20	60	130	1.83 minus	12.05 minus	45.7
J	55	74	217	2.26 minus	17.22 plus	54.5

"ATHLETIC HEARTS" AS DIAGNOSED BY CERTAIN PHYSICIANS

The following points developed in the course of this study.

1. Some physicians, particularly general practitioners, still make the

diagnosis of "athletic heart" with a wide range of meaning, as shown by Fig. 9 in the case of ten of the fifteen hearts so designated. They ranged in area from a deviation of 30.3 per cent plus to 2.26 per cent plus, and from a small, vertical heart, to one with a cardiothoracic ratio of 54.5 per cent and "aneurysmal" dilatation of the aortic arch.

The diagnosis of "athletic heart" is not uncommon, as evidenced by the fact that fifteen in 3000 cases is 0.5 per cent, and that this is essentially the frequency of the diagnosis of active tuberculosis among college students. It should also be noted that the diagnosis of "athletic heart" is more generally socially acceptable than the diagnosis of tuberculosis or syphilis. It may even carry prestige in some circles.

2. It is apparently "normal" for the hearts of successful American Olympic team wrestlers and their alternates to average 26 per cent plus in cardiac area two days after successful final tryouts. Ten of thirteen hearts were increased in size. All but one had potential heart disease factors, and one had right-sided cardiac dilatation. The cardiac enlargement may have resulted partially from heavy fluid intake after temporarily breaking training, with its excessive dehydration incident to reducing to lower weights.

MILITARY ASPECTS

This study does reveal definitely the fact that there are many injured hearts among athletes before, during, and after competition. This fact may explain military rejections of athletes who are popularly considered normal. It is natural for a layman to hold the opinion that athletes are rejected from military service because of "athletic heart," but this is not the case. They are rejected because of organic heart disease of varying degree.

If military standards of heart size alone, without other evidence of cardiac abnormality, were strictly adhered to, some athletes would not be accepted for military service. My personal feeling is that every one of them, except those with definitely organic disease, could be accepted and would perform in a normal, and perhaps above normal, way in military service. The most practical aspect is the possibility that these hearts, whether physiologically or potentially pathologically enlarged, are not as acceptable for aviation at the higher flying levels.¹³ This needs further investigation because Wearn¹⁴ and others have shown that increase in cardiac size through hypertrophy of muscle fibers is not accompanied by an increase in the number of blood vessels, and therefore constitutes a relative inferiority under conditions such as altitude flying, which necessitates the best possible oxygen supply and utilization. Theoretically, oxygen debt would occur relatively earlier in hearts such as these. In cases of pathologically and potentially pathologically enlarged hearts, cardiac anoxemia would develop earlier than it would in cases of supposedly physiologic cardiac enlargement. These theoretical

considerations may be far outweighed by other intangible factors frequently found in true athletes, such as superior volitional trends and superior competitive spirit.

SUMMARY AND CONCLUSIONS

1. An analysis has been made of cardiac size by comparing orthodiagraphic areas and cardiac diameters with the Hodges-Eyster normal standards in a series of 233 persons selected from 3000 American male athletes. Conclusions from this study follow.

2. Generally, athletes' hearts are larger than nonathletes' hearts.

3. "Nonorganic cardiac enlargement" is probably of little clinical importance, and should be considered normal for athletes. Moderate variations from the *average* heart size in normal athletes, in the absence of other signs of organic heart disease, is of no particular significance. The eventual result of "nonorganic enlargement," however, is not as yet definitely known.

4. According to published standards of heart size, the hearts of many athletes are enlarged.

5. The hearts of persons of "softer type" may change size under athletic strain.

6. It is probably detrimental to the health of persons with organic heart disease to participate in sports.

7. The intangible advantages of true athletic training probably outweigh the disadvantages of moderate, "nonorganic" cardiac enlargement (granting that it does exist); this is important in deciding whether or not athletes are acceptable for aviation or other military service. Such hearts should be considered normal.

8. Participation in sport should be encouraged in every way, but only under alert, accurate, and liberal medical supervision.

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DISCUSSION

DR. PAUL D. WHITE, Boston.—I would like to ask Dr. Wilce whether he believes that a possible factor of cardiac strain which will produce actual cardiac enlargement may be very strenuous effort during an illness. For example, a young football player may conceal an acute respiratory infection, if he can, and engage in a very hard game; I would like to ask Dr. Wilce whether he thinks that such a circumstance may have a deleterious effect.

DR. J. W. WILCE, Columbus.—Thank you, Dr. White, for asking that question, because it gives me a chance to bring out a point which was in my paper, but which I did not have an opportunity to discuss. I have several cases of that kind in my series.

You have in Boston the marathon runner who broke the record after he had just gotten out of bed with influenza. He thought he could run only fifteen miles, but he ran the twenty-five and broke the record. I hope that you will pick him up.

I saw a boy with influenza who was playing in a high school basketball tournament. I was able to get an electrocardiogram on him, and there was slight splintering of QRS. I have not had a chance to follow him up.

However, as a coach, twenty-four years ago, I sent a boy into a football game just after he had influenza. I was able to follow him twenty years later, and he did have a deep Q₂ and evidence of myocardial damage, with no other intervening disease factors.

DR. PAUL D. WHITE.—I have one other comment to make about which I have been in discussion with Dr. Wilce. He himself abstained from speaking of it.

A few weeks ago I received a letter from the *Journal of the American Medical Association*, asking for an answer to a query that has been raised as to the slowness of the heart rate in athletes. It was stated that reference had been made in some lay article to the fact that some mile runners, particularly Cunningham and MacMitchell, had pulse rates at rest that were under 40 normally, and the question was: "Is this possible?"

I had not encountered any normal person with a heart rate under 40, so I began to inquire of authorities, like Dr. Dill and Dr. Wilce, who have had rich experience. The answer from them was that they had not encountered any normal person, athlete or otherwise, with a heart rate under 40.

I pursued the point, and wrote to Cunningham and MacMitchell and got in touch with a few others. Dr. Robinson, who is at the Harvard Fatigue Laboratory, and is a former athletic trainer and a physiologist, sent me word that he had a graphic record of a two-mile runner whose normal resting heart rate had been recorded at 35.

Since then I have heard of three others. Although Cunningham has written to me that his heart rate has not been below 40 per minute so far as he knows, MacMitchell states that his pulse rate has been recorded at 32 at rest, one of the marathon runners, Kelly, has had a pulse rate of 38, and Dr. Graybiel has recently sent me the electrocardiogram of one of a thousand healthy aviators whom he studied last year which showed a heart rate of 38 at rest.

So, apparently, as in the case of almost all other rules, there are exceptions to this one, and it is really possible to have a normal pulse rate at rest, usually in an athletic person, under 40 per minute. I do not refer, of course, to the very slow heart rate which may be found in extreme inanition or starvation.

I am wondering if anybody else here has had any such experience.

DR. J. W. WILCE.—I was very much interested in your investigation of these distance runners. There was an article in the *Saturday Evening Post* in which a trainer said that this idea about distance running hurting the heart was a lot of poppycock.

I was going to show three hearts of distance runners who, although they were not definitely ill during the running, had such inferiority value factors at the time of their distance running that I certainly postulated bad effects from it. One had an anginal syndrome, one had early cor pulmonale, and the other had rheumatic heart disease.

I am interested in the type of highly specialized athlete that you mention as having an extremely slow heart rate.

The "amateur professionals" represent one very small group of athletes, the average amateurs represent an extremely large group, which includes almost everybody, and the professionals represent another. The closer one gets to the professional group, the more eventual effects one sees, because, obviously, with this group athletics are engaged in more intensively over a longer period of time. I believe that we should address ourselves primarily to those conditions that have to do with the great majority of the youth of the land, and that we should start to pay more attention to potential heart disease factors in diagnosis in the interest of prevention of cardiac injury from sports.

DR. PAUL D. WHITE.—I think we may all congratulate Dr. Wilce on at least the beginning of an attempt to solve a very difficult problem. This study presents further evidence that the normal heart has a wide range. As we have said before, we shall probably never be able to ascertain the exact limits of normal with any absolutely certain degree of accuracy.

EFFECTS OF CHANGES IN VENOUS PRESSURE UPON BLOOD FLOW IN THE LIMBS

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BOSTON, MASS.

IT IS of considerable practical importance as well as of theoretical interest to know whether increasing the venous pressure in a limb by inflating a blood pressure cuff around it increases the blood flow in the limb. Linton, et al.,¹ at the 1940 meeting of this Section, reported that obstructing the venous outflow from the leg of the dog increased the blood flow through the femoral or iliac artery, as measured with the thermostromuhr. In similar experiments, but using the rotameter, Pritchard and his associates² found that blood flow decreased during the period of venous obstruction. We have studied the problem in human beings by four different methods, namely (1) capillary microscopy, (2) venous blood oxygen analysis, (3) skin temperature measurement, and (4) plethysmography.

CAPILLARY MICROSCOPY

The blood flow in the capillaries of the skin of the forearm and nail-fold was observed microscopically^{3, 4} before, during, and after the inflation of a blood pressure cuff around the upper part of the arm to 30 and to 60 mm. Hg. A more objective index of the velocity of blood flow was obtained in some experiments by recording the time required for the gap between two columns of erythrocytes to pass from the arterial to the venous end of the capillary loop.

Twelve experiments were performed on nine normal subjects. Inasmuch as considerable spontaneous variation may occur in capillary blood flow,⁴ at least ten observations were made at each congesting pressure. Confirming the reports of others,^{4, 5, 6} it was noted that uniformly the rate of blood flow in a given capillary decreased upon inflation of the cuff. For example, in one experiment the time required for a gap to traverse the capillary loop was two, three, and seven seconds, respectively, during cuff pressures of 0, 30, and 60 mm. Hg. However, since it was also noted that during the inflation of the cuff many previously invisible capillaries came into view, the results of this method were not accepted as necessarily indicative of the blood flow to the limb as a whole.

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VENOUS BLOOD OXYGEN ANALYSIS

Venous blood was drawn from the median cubital vein at a point on the forearm previously rendered anesthetic by the local infiltration of a 1 per cent procaine solution. The blood was taken in oiled syringes, fitted with needles which were filled to the tip with boiled, 30 per cent potassium oxalate solution (approximately 0.04 c.c.). It was then immediately transferred to a tube under freshly boiled, but cooled, mineral oil, where it was gently stirred to mix it with the anticoagulant. As quickly as possible, the oxygen content was determined in duplicate by the method of Van Slyke and Neill.⁷ Two specimens of blood were obtained, one when there was no venous congestion, and the other at the end of ten minutes' venous congestion produced by inflating a cuff around the upper part of the arm to 60 mm. Hg. Eight experiments were performed on seven normal subjects. In four experiments the hand was excluded from the circulation by inflating a cuff at the wrist to 300 mm. Hg. Uniformly, the samples obtained during venous congestion contained less oxygen than the control specimens (Table I). Since

TABLE I
EFFECT OF VENOUS CONGESTION ON VENOUS BLOOD OXYGEN CONTENT

SUBJECT	VENOUS BLOOD OXYGEN CONTENT C.C. PER 100 C.C.	
	0 MM. HG	60 MM. HG
W. L.	12.21	4.42
	13.80	4.69
C. F.	7.13	3.03
	8.07	3.22
T. M.*	9.75	6.86
	10.81	7.12
H. C.	9.30	8.11
	9.62	8.52
C. O.	7.25	5.70
	7.33	5.74
C. R.*	8.86	6.63
	8.20	6.00
R. W.*	7.06	4.46
	7.00	4.85
	10.23	6.05
	10.60	6.05

*Hand circulation occluded.

Holling⁸ has shown that, under resting conditions, changes in the oxygen content of the median vein blood reflect directly the changes in blood flow, the decrease in oxygen content during venous congestion was accepted as evidence of a decrease in blood flow.

SKIN TEMPERATURE

The temperature of the skin of the extremities was measured by thermocouples attached to the pads of the fingers and toes,⁹ while the temperature of the room was kept as constant as possible. In some ex-

periments, arterial pressure, pulse rate, and rectal temperature were also measured. Twenty-six experiments were performed on eight normal subjects who lay supine in bed while the effects on skin temperature of inflating and deflating a blood pressure cuff above one elbow or knee were observed. The opposite limb served as a control.

When the body was exposed in a cool room, and the limbs were already cool as a result of sympathetic nervous vasoconstriction, venous congestion of one limb did not cause it to become warmer (Fig. 1, Table II). When the body was covered with blankets and heating pads, warm-

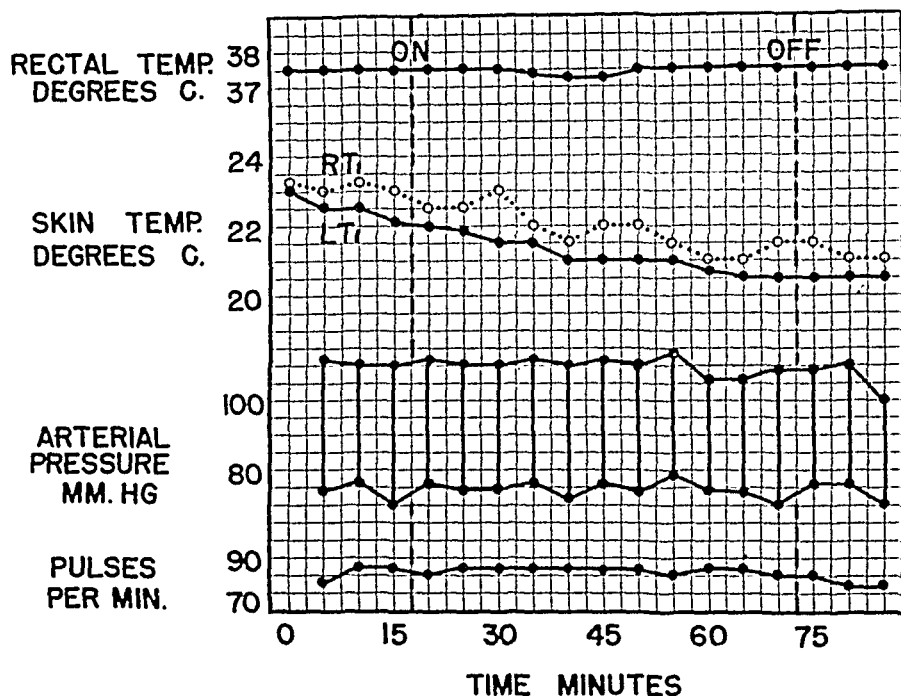


Fig. 1.—Effect of venous congestion upon cool extremities. Chart of rectal temperature; skin temperature of the right great toe (RT_1), and of the left great toe (LT_1); arterial pressure; and pulse rate during an experiment on a normal subject. At 17½ minutes (first vertical interrupted line) a cuff above the right knee was inflated to 50 mm. Hg. At 72½ minutes (second vertical interrupted line) the cuff was deflated.

TABLE II

EFFECT OF VENOUS CONGESTION (50 MM. HG) ON SKIN TEMPERATURE.
SUBJECT COOL

SUBJECT	LEG CONGESTED	DURATION OF CONGESTION MINUTES	SKIN TEMPERATURE DEGREES C.			
			BEFORE		AFTER	
			RT_1	LT_1	RT_1	LT_1
C. F.	R	20	23.7	25.9	23.0	24.7
J. H.	R	40	24.5	24.0	24.6	25.3
A. P.	R	55	23.0	22.2	21.5	20.5
	R	65	21.5	21.0	21.1	20.8
M. C.	R	25	20.1	19.1	20.1	19.5
A. B.	L	10	24.1	24.0	24.1	23.7

TABLE III
EFFECT OF VENOUS CONGESTION (50 MM. HG) ON SKIN TEMPERATURE.
SUBJECT WARM

SUBJECT	LEG CONGESTED	DURATION OF CONGESTION MINUTES	SKIN TEMPERATURE DEGREES C.			
			BEFORE		AFTER	
			RT ₁	LT ₁	RT ₁	LT ₁
C. F.	R	20	32.0	32.0	31.0	32.5
	R	20	34.6	34.5	34.0	34.5
	R	20	32.5	32.0	32.8	34.0
	R	30	34.6	35.0	34.0	35.5
J. H.	R	30	32.6	34.0	32.0	34.8
M. C.	R	25	34.5	34.7	33.0	34.8
A. P.	R	35	34.5	34.8	31.2	34.5
E. P.	R	35	35.0	35.4	35.4	36.0
A. B.	L	40	32.0	33.0	31.8	30.5
C. F.	L	25	35.1	35.5	35.1	35.0
R. W.	L	30	35.0	35.4	35.0	35.0
E. P.	L	30	34.3	35.0	35.5	35.0

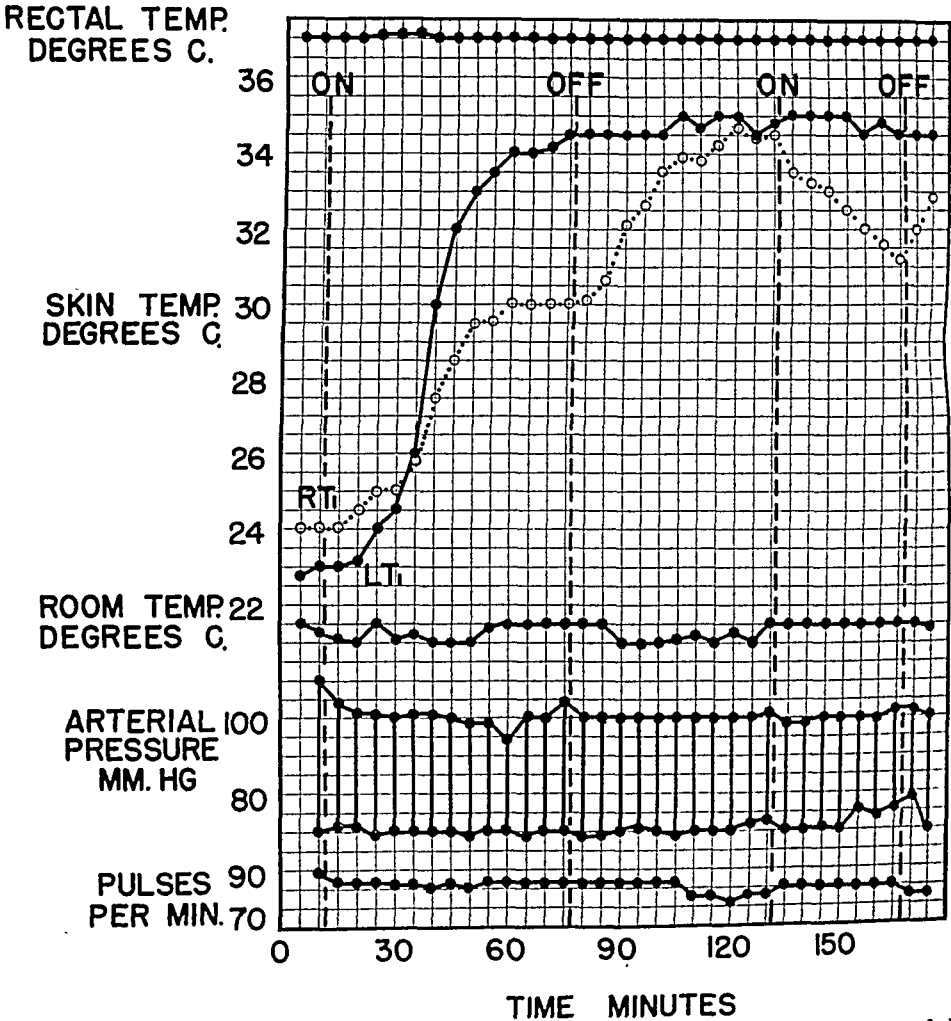


Fig. 2.—Effect of venous congestion upon warming of the extremities caused by sympathetic nervous vasodilatation. Chart of rectal temperature; skin temperature of the right great toe (RT_1), and of the left great toe (LT_1); room temperature; arterial pressure; and pulse rate during an experiment on a normal subject. At the beginning of the experiment the subject was covered with blankets and electric heating pads. At 12 minutes (first vertical interrupted line) a cuff above the right knee was inflated to 50 mm. Hg. At 77 minutes (second vertical interrupted line) the cuff was released; at 132 minutes it was re-inflated, and, at 168 minutes, released.

ing of the extremities as a result of sympathetic vasodilatation occurred; this warming was not accelerated in a congested limb but, on the contrary, was retarded. Furthermore, the congested limb often failed to become as warm as the control limb, although, after release of the congesting cuff, it did become fully as warm as the opposite limb (Fig. 2). When both limbs were already equally warm as a result of sympathetic vasodilatation, venous congestion of one limb did not cause it to become still warmer, but, on the contrary, at times caused it to become somewhat cooler than the control limb (Fig. 2, Table III). In the same manner, while the body was being cooled by exposure, the cooling of the extremities caused by sympathetic vasoconstriction was not retarded by venous congestion, but frequently was accelerated (Fig. 3).

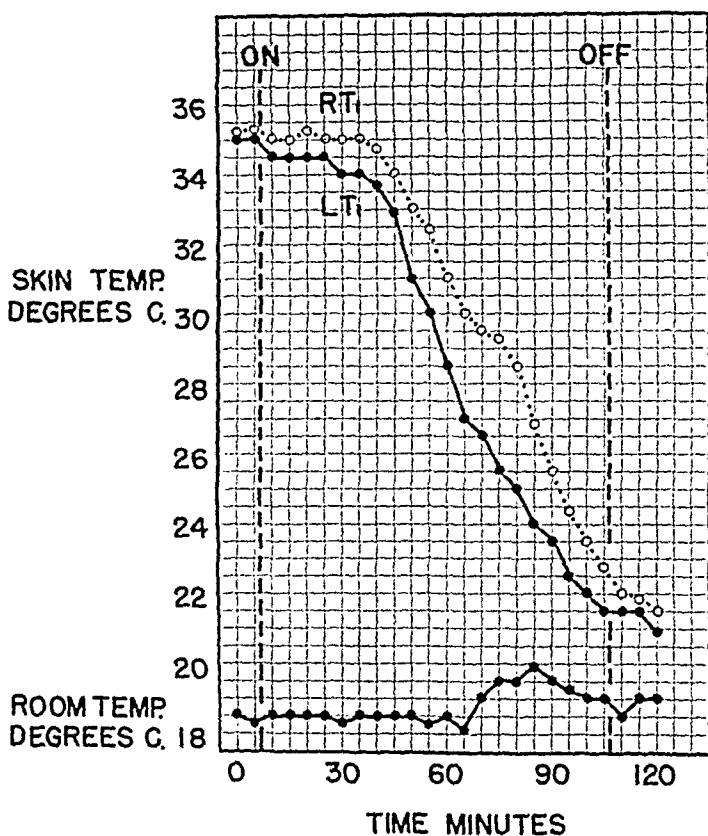


Fig. 3.—Effect of venous congestion upon cooling of the extremities caused by sympathetic nervous vasoconstriction. Chart of the temperature of the right great toe (RT_i), of the left great toe (LT_i), and of the room during an experiment on a normal subject. At the beginning of the experiment the subject was uncovered in the cool room. At 7 minutes (first vertical interrupted line) a cuff above the left knee was inflated to 50 mm. Hg. At 107 minutes the cuff was released.

Finally, observations were made upon the effects of venous congestion on the cooling of the extremities caused by raising them above the horizontal level.^{10, 11} When both feet of a warmed, supine subject were raised 75 cm. above the bed, the toes became cooler. Congesting one leg by inflating a cuff above the knee to 50 mm. Hg did not prevent the

cooling of the foot on that side, but, on the contrary, apparently slightly enhanced the cooling caused by elevation (Fig. 4).

From these results it was concluded that blood flow in the skin of the extremities is not improved, and may be impeded, during venous congestion.

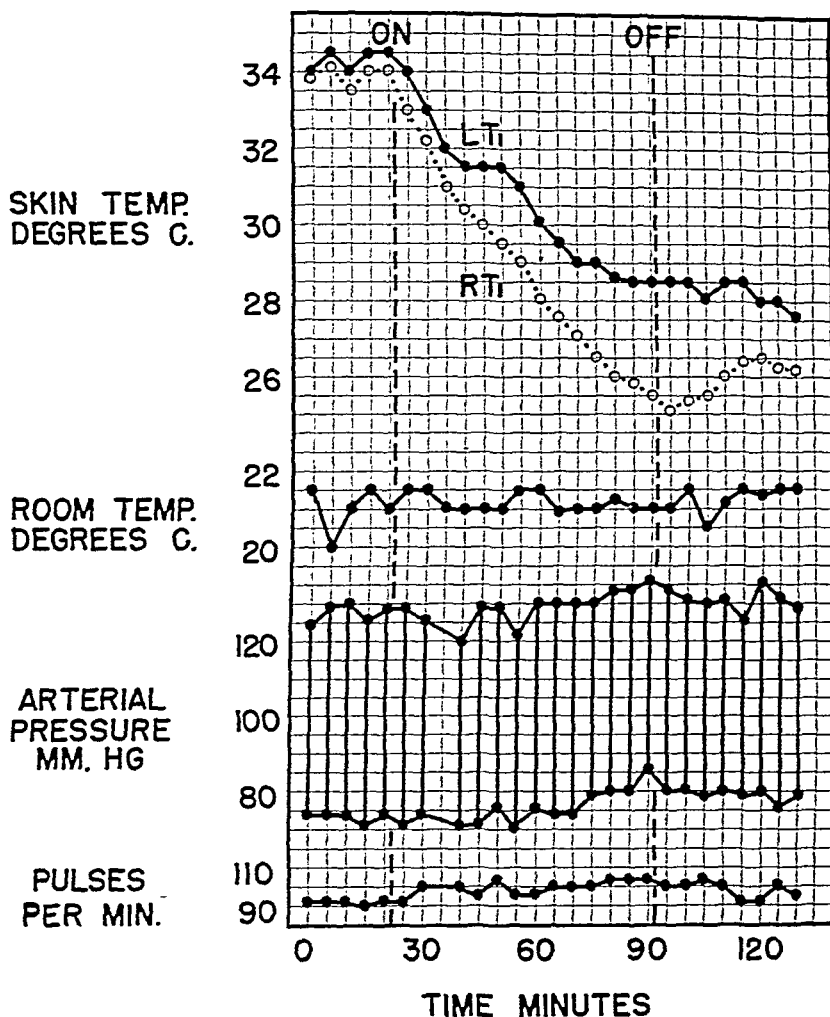


Fig. 4.—Effect of venous congestion upon cooling of the extremities caused by elevating the limbs. Chart of skin temperature of the left great toe (LT_1) and of the right great toe (RT_1); room temperature; arterial pressure; and pulse rate during an experiment on a normal subject. Throughout the experiment the subject was warmed by blankets and electric heating pads. At 22 minutes (first vertical interrupted line) both feet were raised 75 cm. above the bed, and a cuff above the right knee was inflated to 50 mm. Hg. At 92 minutes, the cuff was released.

PLETHYSMOGRAPHY

Evidence concerning the effect of venous congestion upon blood flow to the whole limb (skin and muscle) was obtained by examining the slope of the plethysmographic (Fig. 5) curves recorded during intermittent venous obstruction, i.e., plethysmographic blood flow curves.^{9, 12} The slope of these curves was found usually to rise in a straight line at first, and then to level off with decreasing steepness into a plateau (Fig. 6, upper curve). Except after specific vasodilator procedures, a

slope of *increasing* steepness never occurred, as would have been expected had the rate of blood flow increased during the measurement. Venous pressure, as recorded by the Hamilton method¹³ under similar conditions, always rose promptly upon inflation of the proximal cuff. Hence it was concluded that, as venous pressure rises after inflation of the cuff, blood flow does not increase, at least insofar as one can judge from the slope of the plethysmographic curves. Furthermore, it was shown that the plethysmographic curves were readily capable of indicating an increase in blood flow in the midst of a measurement. Such an increase in blood flow into a proximal part (forearm or calf) was produced artificially by allowing blood from the veins of the distal part (hand or foot) suddenly to escape into the proximal segment. Instead of keeping the cuff just distal to the plethysmograph (Fig. 5) at

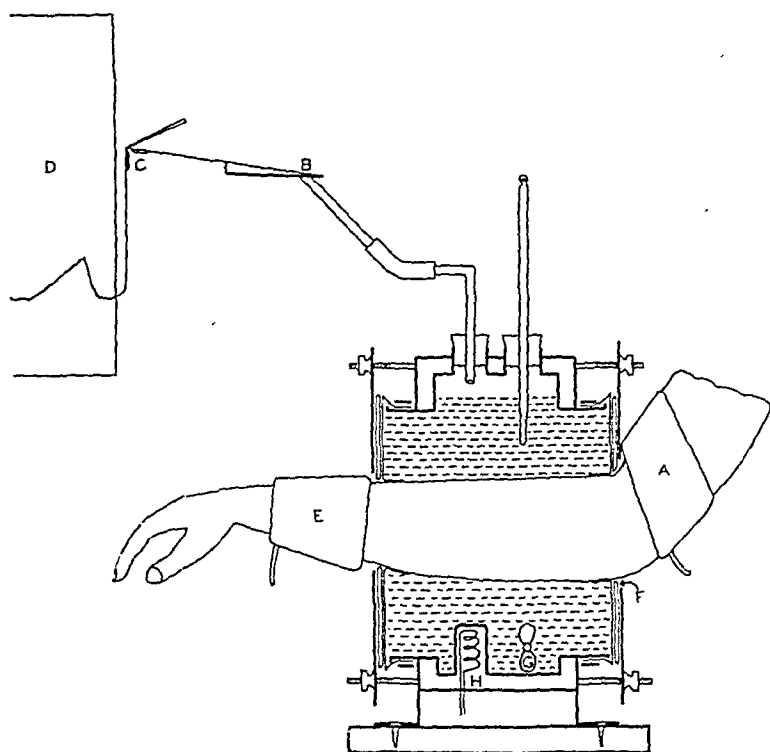


Fig. 5.—Diagram of a segment plethysmograph for the forearm or calf. A is the proximal pressure cuff; B, the Brodie's bellows, with special, hinged writing-lever, C; D, the recording drum; E, the distal pressure cuff; F, the supporting plates; G, the stirrer; and H, the heater.

greater than systolic pressure to exclude completely the circulation in the hand or foot,¹⁴ the distal cuff was so regulated as to permit venous blood from the hand or foot to flow into the proximal segment in the midst of a plethysmographic blood flow measurement. The slope of the plethysmographic curve immediately indicated the additional inflow of blood by a sharp increase in steepness (Fig. 6, lower curve).

Further plethysmographic evidence was obtained by a technique

which allowed measurements of blood flow to be made in a part *during* venous congestion at any desired pressure. Again using the segment plethysmograph (Fig. 5), the distal cuff was first inflated to a pressure considerably less than diastolic, but greater than venous pressure. After a few seconds, as the venous pressure in the part of the extremity distal to this cuff approximated cuff pressure, equilibrium became established.

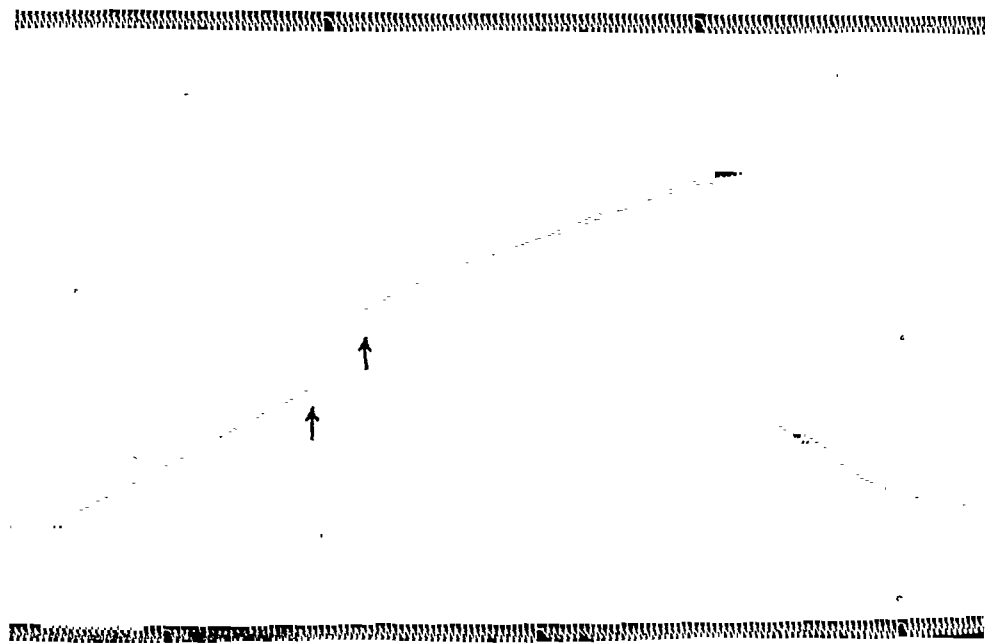


Fig. 6.—Plethysmographic tracings of blood flow to the forearm of a normal subject. The upper curve is of the routine type, obtained with the circulation to the hand occluded by a cuff at the wrist inflated to greater than systolic pressure. The lower curve shows the effect (between the arrows) of allowing blood from the veins of the hand to escape under the wrist cuff into the forearm segment.

This was shown in many experiments by using a second plethysmograph on this distal part to indicate the time at which no further change in volume was taking place. At that time the venous flow from the distal part must have been the same as the arterial flow into it. Moreover,

there was an important difference: the blood flow in the distal part was against a known congesting venous pressure (distal cuff pressure). The venous outflow from the distal part and the arterial inflow to the proximal part were then temporarily trapped within the proximal plethysmograph by intermittently inflating the proximal cuff at a pressure slightly less than that in the distal cuff. Thus, the blood flow both to the congested distal segment and to the proximal segment was measured simultaneously by one plethysmographic curve. As many measurements as desired of these combined flows were made. The pressure in the distal cuff was then raised to a higher pressure, but still less than diastolic, and, after equilibrium had become established, blood flow curves were again obtained from the plethysmograph on the proximal segment. These curves again indicated the sum of the blood flow directly into the proximal segment, and that into (out of) the distal part, which now, however, was congested at a higher venous pressure. Finally, the circulation in the distal part was completely excluded by a pressure in the distal cuff considerably greater than systolic. Blood flow curves then obtained from the proximal segment were considered accurate for that segment alone.^{9, 14} Since the blood flow to such a proximal segment is known to be fairly constant,^{9, 15} the consistent changes which were found in the previous combined flows obtained at different distal congesting pressures were attributed to the differences in the distal congesting pressures.

TABLE IV

EXCERPT FROM A PLETHYSMOGRAPHIC EXPERIMENT. COMBINED BLOOD FLOWS TO THE PROXIMAL (UNCONGESTED) AND DISTAL (CONGESTED) PARTS OF THE UPPER AND LOWER LIMBS OF A NORMAL SUBJECT

PULSE RATE BEATS/MIN.	ARTERIAL PRESSURE MM. HG	PRESSURE IN DISTAL CUFFS MM. HG	BLOOD FLOW C.C./MIN.	
			LEFT FOREARM	LEFT CALF
66	96/68	270	21	37
66	100/66	30	111.5	78
66	96/68	60	69	70
68	98/68	30	118	86
68	98/68	60	51	59
66	100/68	30	92	69
68	98/68	60	57	58

*Circulation in hand and foot excluded.

The average of at least four measurements of blood flow at each level of pressure in the distal cuff was accepted as representative of the blood flow to the part or parts under the experimental conditions imposed (Table IV). Although there was some variation between individual measurements, there was no uniform tendency toward either an increase or a decrease in blood flow as any given pressure in the distal cuff was prolonged up to ten minutes. Allowance was made in the calculations for the blood flow to the small segment directly under the distal congesting cuff, by subtracting from the combined flows at the

lower congesting pressure an amount (5 c.c.) greater than the estimated flow in the part under the cuff without any pressure. This was done because, in other experiments, it was shown that local pressure on a limb, as from an inflated cuff, greatly reduces the blood flow in the part under pressure.

Twenty experiments were performed on nineteen different subjects, a few of whom had peripheral vascular disease. The subjects lay supine with their limbs at heart level, and were comfortably warmed by blankets and heating pads to produce generalized peripheral vasodilatation.⁹ The pulse rate was counted from the plethysmographic tracings, and the arterial pressure was measured in a free limb by the usual auscultatory method.

TABLE V

EFFECT OF CHANGES IN DISTAL CUFF PRESSURE UPON COMBINED (PROXIMAL AND DISTAL) BLOOD FLOWS

CUFF PRESSURE		COMBINED BLOOD FLOW					
CHANGE	INSTANCES	INCREASED		NO CHANGE		DECREASED	
		INSTANCES	%	INSTANCES	%	INSTANCES	%
Increased	114	9	8	8	7	97	85
Decreased	84	67	80	9	11	8	9

As is shown in Table V, increasing the congesting pressure in the distal cuff reduced the combined flows in 85 per cent of the tests, whereas decreasing the congesting pressure increased the combined blood flows in 80 per cent of the experiments. Discrepancies in the results were only to be expected, for it has been shown that considerable spontaneous variations may occur in blood flow, especially to the distal parts of the limbs.¹⁴

DISCUSSION

In 1925, Lewis and Grant¹⁶ reported that "when the arterial supply to a limb is occluded and released a state of vasodilatation is found," and that "a similar reaction occurs when venous pressure is increased." Further, they reported that "the reaction is not a response of the vessels to change of pressure within them, it is related to blood-flow debt"; and that, "the loss of vascular tone, which is responsible for the vasodilatation, occurs during the period of circulatory standstill or slowing."

As evidence for the latter statement a number of observations were reported, one of which was that, after ten to fifteen minutes of venous congestion at 40 to 50 mm. Hg, an increase was found in the amplitude of the pulsations recorded plethysmographically from the congested part.* This suggested to Lewis and Grant "that venous engorgement

*We have never observed an increase in the amplitude of the plethysmographic pulse waves during venous congestion similar to that illustrated in Lewis and Grant's article. This may be due to the fact that, during our experiments, greater precautions were taken to control the state of sympathetic nervous vasodilatation.⁹ However, we do not doubt that a decrease in vascular tone does take place during the slowing of blood flow due to venous congestion, and that it might contribute to an increase in amplitude of the pulsations in the congested part.

causes dilatation of the vessels on the arterial side," although they gave no more direct evidence for this belief. It is important, however, to note that Lewis and Grant did not state, or intimate, that venous congestion in a limb is associated with an increase in blood flow over the resting (uncongested) level. On the contrary, they distinctly stated, as pointed out above, that the loss of vascular tone occurs during the period of circulatory *slowing*, and is related to blood flow *debt*. In other words, they believed that this reaction, like that to circulatory standstill from arterial occlusion, is a compensatory response to blood flow deprivation. Nevertheless, their work has been cited in support of the view that venous congestion in a limb may augment the arterial inflow to the limb.^{1, 17}

It is unfortunate that the words "reactive hyperemia" have been used in connection with the loss of vascular tone that occurs during the period of circulatory arrest or slowing, for the term, strictly speaking, refers only to the increase in blood flow which follows the release of such an arrest or slowing. Obviously, "loss of vascular tone" and "hyperemia" (increase in blood flow) are not necessarily synonymous terms, particularly when there is a local obstruction in the circulation sufficient to retard the blood flow, even in vessels of low tone. A failure to appreciate this distinction of terms perhaps has contributed to the confusion that has arisen.

Hydrodynamically, it seems impossible that an increase in the flow of fluid through a collateral system of elastic tubes could occur when the egress of the fluid from the system is obstructed. This view has been substantiated in our laboratory by means of a mechanical schema constructed of various types of rubber tubes to represent arteries, arterioles, capillaries, and veins. With a constant head of perfusing pressure, any elevation of "venous pressure," produced either by exerting pressure upon the large collapsible tubes representing the veins, or by raising the outflow level of these tubes, was accompanied by a decrease in flow through the schema.

Inasmuch as considerable criticism has been directed at the methods which apparently have revealed that an increase in blood flow occurs in vivo during venous congestion of a limb, we did not rely on a single method, but used four different types of measurements. The results show clearly and uniformly that blood flow does not increase in the limbs of human beings during rises of venous pressure produced by inflating blood pressure cuffs around them, but, on the contrary, usually decreases.

Concerning reactive hyperemia after the release of venous congestion in a limb, it undoubtedly occurs; however, it is quite small in amount and short in duration when compared with the reactive hyperemia which follows the release of arterial occlusion.¹⁶ In the limbs of patients with severe obliterative arterial disease, the mechanism of reactive hyperemia is apparently being constantly invoked. This is shown by the fact that occlusion of the circulation is not followed, upon release, by any increase

in blood flow over the resting level.¹⁸ It would seem that in such limbs there is always as much vasodilatation as is structurally possible under the stimulus of blood flow deprivation. These observations demonstrate the impossibility of improving the circulation in these limbs by reactive hyperemia, especially that which follows the release of venous congestion, which even in normal people is relatively slight.

Because of these considerations, we have not deemed it wise to use venous congestion over long periods of time in the treatment of patients with obliterative vascular disease. Hence, we have no observations upon its therapeutic effects in such cases. Furthermore, we did not wish to consider the variable ingrowth of collateral circulation in limbs after peripheral vascular accidents, because this would only have complicated the main problem we undertook to solve, namely, the effect of venous obstruction upon blood flow through a given vascular tree.

SUMMARY AND CONCLUSIONS

The blood flow in the extremities of human beings was measured with and without local venous congestion produced by inflating blood pressure cuffs on the proximal parts of the limbs. Four different methods were used: capillary microscopy, venous blood oxygen analysis, skin temperature measurements, and plethysmography. By all methods it was found that blood flow is not increased in the limbs during rises of venous pressure, but, on the contrary, is usually decreased.

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DISCUSSION

DR. EDGAR V. ALLEN, Rochester, Minn.—It seems to me that Dr. Wilkins' paper is a very good illustration of how dependent the clinical practice of medicine is on such excellent studies in the laboratory. It also seems to me to represent a return to reason and to logic, because I am sure that it could never appeal to reason and logic to say that the arterial blood flow increased during a period of venous constriction. There is adequate evidence, I believe, to indicate the incorrectness of observations reported previously before this society that, using the thermostromuhr, one could demonstrate actual increase of arterial blood flow during venous compression.

It is only fair to point out that Dr. Wilkins has not said that repeated intermittent venous occlusion fails to increase the blood flow. He has said, however, and shown very conclusively, it seems to me, that, during the period of venous obstruction, there is no increase in the arterial blood flow.

Perhaps Dr. Wilkins has some evidence—I am sure he has—to indicate that which seems to be true also; that is, if one occludes the venous blood flow to the extremities intermittently, there is likewise no increase in the blood flow. I hope that he will comment on that.

DR. ROBERT R. LINTON, Boston.—I think I should say a word, inasmuch as I read the paper here two years ago.

The method of measuring blood flow with the thermostromuhr is, of course, a direct method. Whether it is an accurate method of measuring blood flow, I am not exactly sure, but I believe it indicates fairly accurately changes in blood flow, that is, whether it increases or decreases in volume. The data reported here today indicate blood flow-only by inference.

Whether or not there is an increase or decrease with intermittent or complete venous occlusion of the main concomitant vein may still not be settled, but I think for clinical use venous occlusion is a very important adjunct in the treatment of peripheral arterial disease. In our experience it has been of little value in chronic obliterative arterial disease, but in acute arterial occlusion it is of inestimable value. I should like to cite a case of the latter.

A woman, 50 years of age, came in with a large carcinoma of the ovary, which I had to resect. In resecting it, I ligated her internal iliac artery. I did not realize at the time that I had damaged her external iliac artery, or I would have done a sympathectomy to improve the collateral circulation. Thinking I had not damaged her external iliac artery, I thought her leg would be all right. I saw her again an hour after the operation, at which time she was perfectly conscious. She said, "Doc, my foot is dead." And it was dead; you could stick pins into it. It was just as white as a sheet. No arterial pulsation or oscillations could be made out. The only thing I could think of for treatment was intermittent

venous occlusion. I applied a pressure cuff as high up on her thigh as possible. I inflated it to 50 mm. Hg. At the end of nine minutes there was a little color in the tips of her toes. We did not have a machine which would give a nine-minute period of occlusion, so for the next forty-eight hours I had the special nurses inflate the blood pressure cuff to 50 mm., leave it so for nine minutes, and then release it for one minute. At the end of that time we were able to decrease the "on" period so that we could use the machine.

In three weeks the patient was able to walk out of the hospital and is still walking on her leg, which is a perfectly good leg. It is not as good a leg as it was originally, but she can walk a mile without much difficulty, and the leg to outward appearances is perfectly normal. There are still no pulses palpable in it.

I just cite this case to impress upon you that intermittent venous occlusion, despite the laboratory evidence presented here today can be used to save extremities following acute major arterial occlusion to a limb.

DR. GEZA DE TAKATS, Chicago.—I agree with Dr. Linton that the clinical value of intermittent venous occlusion is very definite. I have no data to show whether or not the blood flow actually increases through the obstructed limb, but for some time we have maintained—and Dr. Linton has given experimental evidence of it—that there is a mechanical filling and stretching of the venous-capillary bed when the arterial flow is unobstructed and the venous flow is obstructed. I have always felt that that is the real cause of the clinical improvement we see; for the support of this contention we have published oscillometric curves, J. A. M. A. 108: 1951, 1937.

DR. EDGAR V. ALLEN, Rochester, Minn.—It seems unwise to speak twice, but I cannot let pass without some comment what Dr. Linton has said relative to the use of intermittent venous occlusion for acute arterial occlusion. I am quite sure he did not want to imply, because of his experience in one case, that intermittent venous occlusion or venous occlusion of any type would save an extremity afflicted with sudden arterial occlusion.

Halsted showed many years ago that, if the iliac artery was ligated, there was complete recovery in almost all of the cases, even when no treatment was given. Gangrene ensued very rarely. These statements apply to ligation of the subclavian artery. It is true, therefore, that one may ligate the major arteries to the extremities with an extremely small incidence of gangrene.

Even in arterial embolism, in which the situation is substantially different because of the great arterial spasm which results from it, the incidence of spontaneous recovery is about 50 per cent without any treatment whatsoever.

So it would take more evidence, I believe, than one case or ten or more cases could furnish, to show that venous occlusion will save the extremity when its arterial circulation has been jeopardized by ligation of the chief artery.

DR. WILLIAM S. COLLENS, Brooklyn.—I should like to ask Dr. Wilkins whether he doubts the existence of the phenomenon of reactive hyperemia which follows the release of venous congestion. I saw no evidence of this phenomenon in his presentation.

Although Dr. Wilkins has demonstrated that venous congestion slows the circulation, one must be careful to interpret its clinical implications. I sometimes wonder whether laboratory evidence indicating the existence of a slowing of the circulation by venous congestion is necessarily a criterion with which to condemn intermittent venous occlusion as a therapeutic procedure.

When I ask that question I have in mind the work of Landis, with his evidence of an increase in capillary pressure that is associated with the state of venous congestion and an increase in capillary pressure after the release of venous congestion. I believe that these increases in capillary pressure produced by inter-

mittent venous occlusion in patients with arterial impairment favor the diffusion of nutrient substances from capillary to cell and aid in the healing of lesions. Obviously, this investigation does not tell the whole story.

As you know, Dr. Wilensky and I have for some years been proponents of intermittent venous occlusion therapy. As the years have gone by, we have continued to investigate the problem clinically. Since Dr. Linton has described to you one case, and Dr. Allen has criticized an experience with only one case, let me say that we have already had experiences in well over five hundred cases. When we try to remain unbiased and observe the patients during a control period without intermittent venous occlusion therapy, and then observe the sudden changes which are produced by the use of this therapy in patients with chronic obliterative disease, we become convinced very frequently that perhaps there is justification for intermittent venous occlusion therapy.

DR. ROBERT R. LINTON, Boston.—This [drawing on blackboard] is the aorta. This is the common iliac artery [indicating]. These are the external and internal iliac arteries [indicating].

I agree with Dr. Allen that Halsted's statements are perfectly true, i.e., if you tie the common iliac, the danger of gangrene in the extremity is not great in a young individual. One point that Dr. Halsted did not make, however, was that if you ligate the internal and the external iliac arteries, it is much more serious than if you ligate only the common iliac or the external iliac.

If you examine the vascular tree, you will see why that is true. If you tie the common iliac, the collateral circulation can get into the external iliac and down the leg through the internal iliac artery.

The reason I cited this case was merely to show that in an extreme case of vascular occlusion, when both the internal and external iliac arteries were occluded, the extremity was saved with intermittent venous occlusion when properly carried out. I have had other cases which proved the same thing, and I still feel that intermittent venous occlusion has a definite use in acute arterial occlusion.

DR. NATHAN D. WILENSKY, Brooklyn.—I should like to ask Dr. Wilkins whether he has employed his technique and made observations on patients with peripheral arterial disease with arterial impairment, using between 30 and 40 mm. of pressure and between one and two minutes of venous congestion.

DR. IRVING S. WRIGHT, New York.—I cannot let this discussion go by without saying that we conscientiously tried the use of this apparatus in twenty-eight cases over a period of one year, at the Post Graduate Hospital, and gave it up. This we would not have done if we had been convinced of its value.

DR. J. MURRAY STEELE, New York.—It seems to me that there are two quite distinct points in connection with this question. The paper under discussion was an attempt to answer the question whether or not, when one occludes the circulation with moderate pressure in a cuff, the circulation increases at the time the pressure is elevated. From another point of view, because this particular procedure has been used clinically, another question arises, namely, whether intermittent venous occlusion is good or bad for people with poor arterial supply. The two problems are quite distinct.

DR. NATHAN D. WILENSKY, Brooklyn.—The question whether improvement in circulation occurs with venous occlusion has still not been answered by these experiments. Although Sir Thomas Lewis demonstrated that a period of hyperemia follows the release of venous congestion, Wilkins does not present evidence that this phenomenon occurs. Yet we believe that the therapeutic rationale of venous occlusion lies in the production of reactive hyperemia.

Our therapeutic procedure did not allow for periods of congestion as long as ten minutes, for we found that the application of a congestive cuff to a limb

with an open lesion for this period of time could not be tolerated by the patient. We found it necessary to shorten the congestive period to about two minutes. In our original publication we reported on the use of two minutes of congestion and two minutes of release. We were convinced of the clinical value of this procedure and evidence of improved circulation by the relief of the patient's symptoms and the healing of ulcers.

DR. ROBERT W. WILKINS, Boston.—I am sorry that, despite our deliberate attempt to keep this presentation on a scientific basis, we seem to have entered the realm of feeling. I noticed how many times the words "I feel" and "I think" have been used. We really would prefer not to "feel" either way about it.

I should like to answer the questions in the reverse order from that in which they were asked, because that will keep the more recent discussions in our minds.

In regard to Dr. Collens' and Dr. Wilensky's objection to accepting laboratory evidence in therapeutic practice, it is a valid objection provided one doesn't call in any laboratory evidence, as, for example, Sir Thomas Lewis' or Landis' studies on reactive hyperemia. We are perfectly aware that reactive hyperemia occurs, and have published an extensive study on this subject. In Sir Thomas Lewis' original paper he used the term "reactive hyperemia" to indicate the reaction that occurs in a limb after deprivation of blood flow. It is a repayment, so to speak, not a thing which comes out of the blue; it occurs only after one first deprives the limb of its circulation.

I was most interested in Dr. Wilensky's comments as to the inability of a patient with acute obstruction of the circulation to tolerate long periods of venous obstruction, because I presume that he meant that it was clinically unpleasant or intolerable for the patient to undergo this procedure for a period of any duration. That, to me—if one wishes to accept only clinical evidence—would indicate that the blood flow, or, at least, the nourishment of the tissues during that period was impeded, and not enhanced.

We have used periods of venous obstruction of one or two minutes. We have also used longer periods. Dr. Linton, as you know, advocates the longer period. Dr. Collens and Dr. Wilensky advocate the shorter period. In our physiologic studies we have found no significant difference in the results, regardless of whether the pressure is used for longer or shorter periods of time.

We have used a pressure as low as 20 mm. Hg. We wish to emphasize, however, that these lower pressures produce little, if any, decrease in blood flow—in fact, little result whatever.

Returning to the matter of reactive hyperemia, if one wishes to produce reactive hyperemia in a limb, the best way to do it is to shut off the arterial inflow completely by a high cuff pressure. When you say "reactive hyperemia," as I pointed out a moment ago, you imply that the limb and its circulation are reacting to a period of blood flow deprivation. Katz and his associates have shown that a number of patients with obliterative vascular disease have, in a sense, a constant reactive hyperemia in their limbs, because, when one occludes the arterial circulation and then releases it, no reactive hyperemia, that is, no increase in blood flow over the resting level, occurs. Therefore, it would appear that these people have as rapid a blood flow as they can have, that the mechanism of reactive hyperemia is being constantly invoked, and that doing anything further with the hope of getting overpayment of the debt is of little value. In regard to the overpayment of the oxygen debt or of the blood flow debt by reactive hyperemia, most of the laboratory evidence would indicate that the debt is not overpaid. In fact, it is somewhat underpaid.

I have no comment on Dr. deTakats' question about the mechanical filling of the venous-capillary beds.

And that brings us to the final point, that Dr. Steele so nicely summed up for us, as to whether the results of this study can be brought to bear on the therapeutic value of intermittent venous occlusion in the treatment of peripheral vascular disease. Now, obviously, we did not wish to go beyond the conclusions of our experiments, but the implications are clear, and they have been taken by both those on the defense and those on the offense.

In response to Dr. Allen's question, we have not found that longer periods of intermittent venous occlusion are followed by an increase in resting blood flow after either one or many periods of occlusion. Naturally, we would have to carry on such experiments for days, and that brings in a very important point. We don't know whether there is a mechanical filling and emptying of the venous-capillary beds that is important. There may be. We did not want to consider whether ingrowth of collateral circulation would be promoted. Again, we have considered such an ingrowth to be a response to a deprivation of blood flow. Finally, we have no evidence on one very important point, namely, the lymphatic drainage from these limbs, which might conceivably be enhanced with the intermittent tension and relaxation of the limb as a whole, before and after venous obstruction.

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

I. EFFECTS ON THE MYOCARDIAL CELLULAR STRUCTURE*

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THESE studies were undertaken to ascertain (1) whether doses of digitalis, which were calculated to be equivalent to those administered clinically, produced demonstrable histologic changes in the myocardiums of experimental animals and (2) what is the minimal amount of digitalis (and its relation to the quantity of the drug used clinically) which will produce anatomic changes in the myocardiums of laboratory animals.

LITERATURE

Several investigators have reported that digitalis bodies are capable of producing organic changes in the myocardiums of animals. Levitski¹ administered galenical digitalis preparations and digitoxin in single and multiple doses to rabbits, dogs, and cats; he observed focal degenerative lesions in the myocardial fibers and evidence of inflammation in the connective tissue of the damaged hearts. Büchner^{2, 3} described cellular changes in the hearts of the experimental animals on which Bauer and Fromherz⁴ and Bauer⁵ had studied certain cumulative phenomena produced by digitalis (digitoxin), gitalin, and strophanthin). The focal degenerative and exudative changes were essentially the same as those described by Levitski. Büchner pointed out that the lesions appeared three or more days after the digitalis had been administered, that they showed a predilection for the left ventricle, and that their origin was most likely related to a disturbance of the blood supply to the myocardium. He stated that these histopathologic changes are similar to those which occur in the myocardiums of patients who die shortly after an attack of angina pectoris⁶ and to those in the hearts of rabbits after artificially induced anemia and strenuous exercise.^{7, 8} Attention was called to the striking similarity between an attack of angina pectoris in man and the crying out and the motionless attitude assumed by cats after intravenous injections of digitalis. Weese and Dieckhoff⁹ also reported cardiac lesions after the administration of toxic doses of digitoxin. The lesions were found in cats, but not in dogs and rabbits.

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Hu, Lieu, and Li¹⁰ found anatomic lesions in the hearts of dogs (seventeen out of nineteen) which had received daily intravenous injections of digitoxin or lanadigin. Since these authors could not produce histopathologic changes in the myocardium of the frog, which does not have any coronary circulation comparable to that found in mammals, they concluded that digitalis bodies must bring about the myocardial lesions in the dog by constricting the coronary arteries. Lindner¹¹ observed histologic changes in the myocardium of the cat after the administration of digitoxin and oleandrin. He assumed that these lesions were primarily the result of metabolic changes in the myocardium and not of circulatory disturbances.

It is not clear from the work of the aforementioned investigators how the doses of digitalis bodies which produced anatomic changes in the myocardiums of experimental animals compared, on the basis of body weight, with those used clinically. The data to be presented in this paper throw some light on this question.

METHODS

Cats were used in these studies on the effects of digitalis on the cellular structure of the heart. Each animal was trained to lie quietly on its right side while electrocardiograms were taken. A control tracing was made each day until its contour remained fairly constant,¹² and until the animal was trained satisfactorily.

The animals were then weighed carefully, and the proper amount of digitalis was administered either by stomach tube or by intravenous or intramuscular injection. The dose of digitalis (or its glucosides) for each animal was calculated on the basis of percentage of the minimal lethal dose for the cat. Thirty per cent of the minimal lethal dose for the cat was assumed to be approximately equivalent to the therapeutic dose used in man. The cat unit served as a basis for the comparison of the dosage of digitalis for man and the cat. Eight different digitalis preparations were used: (1) digiglusin, ampule preparation of digitalis for parenteral administration; 1 c.c. was equivalent to 1 Hatcher-Brody cat unit; (2) digalen, ampule preparation of digitalis for parenteral administration; 2 c.c. were equivalent to 1 Hatcher-Brody cat unit; (3) digifoline, ampule preparation of digitalis for parenteral administration; 2 c.c. were equivalent to 1 Hatcher-Brody cat unit; (4) digifortis, tincture of digitalis for oral administration; 1 c.c. was equivalent to approximately 11½ Hatcher-Brody cat units; (5) digitoxin, crystalline preparation; minimal lethal dose = 0.42 mg. per kilogram of cat (Hatcher-Brody method); (6) lanatoside A, crystalline preparation; minimal lethal dose = 0.35 mg. per kilogram of cat (Hatcher-Brody method); (7) lanatoside B, crystalline preparation; minimal lethal dose = 0.60 mg. per kilogram of cat (Hatcher-Brody method); and (8) lanato-side C, crystalline preparation; minimal lethal dose = 0.25 mg. per kilogram of cat (Hatcher-Brody method).

At various intervals after these drugs had been administered, observations were made on the behavior of the animals, frequent electrocardiograms were taken,¹² and finally those animals which did not die spontaneously were killed by placing them in a closed chamber and permitting them to breathe concentrated fumes of ether or chloroform. Necropsies were performed immediately. The brain and spinal cord were removed first.¹³ Blocks of tissue from the heart were fixed in a 10 per cent solution of formalin after they had been removed from the following regions: (1) the anterior papillary muscle and the left ventricle wall, (2) the pos-

terior papillary muscle and the left ventricular wall, (3) the interventricular septum, (4) the right ventricular wall, (5) the right auricle or atrium, and (6) the left auricle or atrium. After proper fixation, these blocks of tissue were embedded in paraffin, sectioned, and stained routinely with hematoxylin and eosin. Some of the sections were stained with sudan III or Mallory's connective tissue stain. From each block of myocardium an average of six to twelve sections were made transversely (at right angles to the direction of the main muscle bundles), and a similar number of sections were made longitudinally (parallel to the direction of the main muscle bundles). An attempt was made to have the sections pass from the endocardial to the epicardial surfaces of the heart. An average of ninety-six sections were examined from each heart.

Blocks of tissue from the skeletal musculature (biceps, abdominal wall, and diaphragm), smooth musculature (stomach, duodenum, ileum, and uterus), kidney, and liver were fixed in a 10 per cent solution of formalin, sectioned, and stained. These tissues were examined routinely in each control animal and every animal which received digitalis.

The control animals were treated exactly like the experimental animals except that the controls did not receive digitalis. One control animal was killed for approximately every four experimental animals throughout the course of the studies.

RESULTS

A. Anatomic Studies of the Myocardiums of the Control Animals.—All of the cats which were used as controls were apparently in good health. The only abnormality found in the hearts of these animals was an occasional, fresh, subendocardial hemorrhage; it is possible that these hemorrhages were caused by the sudden death which was produced by ether or chloroform.

There were no macroscopic or microscopic evidences of any abnormality of the pericardium, the myocardium, or the coronary vessels in any of the control animals.

B. Anatomic Studies of the Myocardiums of Animals Which Had Received Therapeutic Doses of Digitalis.—Two types of experiments were designed to ascertain the effects of calculated therapeutic doses of digitalis on the anatomic structure of the heart. To one group of animals (Group A), the calculated therapeutic amount of the drug was administered in a single dose within a period of two to three minutes, or it was given in divided doses over a period of twenty-four to forty-eight hours; the myocardiums of these animals were examined microscopically from six to fifty-six days after the drug has been administered. To the other group of animals (Group B), the calculated therapeutic dose of digitalis was administered as in Group A, but, in addition, a daily estimated maintenance dose was given to the animals over a period of nineteen to sixty days. The maintenance dose was chosen arbitrarily on the basis of the body weight of the cat as compared with that of a man weighing 70 kg. For example, if 0.1 Gm. (1 cat unit) of digitalis whole leaf is the average daily maintenance dose for a man weighing 70 kg., a seventieth of 0.1 Gm. (or 0.00143 Gm.) was taken as the daily maintenance dose for each kilogram of cat. It is appreciated that this assumption is open to criticism (see consideration

of sources of error under "comment"). The hearts of the animals in Group B were examined histologically nineteen to sixty days after the administration of the digitalis bodies had been started.

TABLE I
ADMINISTRATION OF CALCULATED THERAPEUTIC DOSES OF DIGITALIS
GROUP A

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Lanatoside A	20	Single dose, intravenous	14
Digalen	20	Single dose, intravenous	15
Digalen	30	Single dose, intravenous	6
Lanatoside C	30	Single dose, intravenous	11
Digitoxin	30	Single dose, intravenous	11
Lanatoside A	30	Single dose, intravenous	12
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12
Lanatoside A	30	Divided doses (48 hr.), intravenous	12
Digalen	30	Single dose, intravenous	14
Digitoxin	30	Single dose, intravenous	14
Lanatoside A	30	Single dose, intravenous	18
Lanatoside A	30	Single dose, intravenous	21
Digifortis	30	Single dose, oral	56

In Group A there were thirteen cats (Table I). No anatomic changes were observed in the hearts of any of the animals which had received a calculated therapeutic dose of digitalis. In the majority of the experiments the myocardium was examined within one to two weeks after the drug had been administered, for, as will be shown later, this is the time during which cellular changes are most likely to be found after the administration of a single toxic dose of digitalis.

In Group B there were eleven animals (Table II). The purpose of the experiments in this group was to ascertain whether, in digitalized animals which are receiving daily maintenance doses of the drug within the range of dosage used in man, demonstrable morphologic changes in the myocardium would develop. Five of the animals, which were first digitalized with a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose), received daily maintenance doses that were estimated to be the approximate equivalent in the cat of 1 cat unit daily for a man weighing 70 kg. The remaining six animals were also digitalized with 30 per cent of the minimal lethal dose of the drug, and then given daily the estimated equivalent of 2 cat units. The weight of a 70-kilogram man and the body weight of the cat were again used as the basis for the calculation of this daily dose.

In none of the animals in Group B did definite cellular changes in the myocardium develop, even when the digitalis was administered daily for periods as long as two months. All the animals tolerated the maintenance dose well except one cat which received digalen over a period

of forty days; in this case anorexia developed, and the animal lost weight during the last three weeks of administration of the drug.

TABLE II

DAILY ADMINISTRATION OF THE EQUIVALENT OF 1 OR 2 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED WITH 30 PER CENT OF THE MINIMAL LETHAL DOSE
GROUP B

DRUG USED	DAILY EQUIVALENT DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Digalen	1	Intravenous	19
Digifortis	1	Oral	19
Digifortis	1	Oral	30
Digalen	1	Intravenous	34
Lanatoside A	1	Intravenous	36
Digiglusin	2	Intravenous	20
Digifortis	2	Oral	30
Digalen	2	Intravenous	30
Lanatoside A	2	Intravenous	36
Digalen	2	Intravenous	40
Digifortis	2	Oral	60

C. Anatomic Studies of the Myocardiums of the Animals Which Had Received Toxic Doses of Digitalis. (a) Observations correlating dosage, duration of experiment, and histologic studies of the myocardium. It was difficult to group the animals in this series of experiments, for the number of animals was rather large and the manner in which the digitalis bodies were administered varied considerably. Perhaps it would simplify the presentation if one arranged the animals in this series into two major groups: (1) Group A₁, those animals which received a single toxic dose of digitalis and subsequently had the myocardiums examined microscopically after various periods of time; (2) Group B₁, those animals which received multiple doses of digitalis in various toxic amounts over different periods, and then had their hearts subjected to histologic study.

In order to ascertain approximately the smallest amount of digitalis, as well as the minimal time, necessary to produce these anatomic changes in the myocardium, a series of animals was given digitalis (or one of its glucosides) in single doses, varying from 20 per cent to 80 per cent of the minimal lethal dose. The animals were killed at various periods after the drug had been administered, and the myocardiums studied histologically.

Table III shows the amounts of the various single doses of digitalis bodies, the route of administration, the duration of the experiment after the drug was administered, and the results of the histologic examination of the myocardium. The data summarized in Table III indicate the following:

1. No demonstrable anatomic changes were observed in the myocardium after the administration of either 40 or 50 per cent of the minimal lethal dose.

2. Demonstrable histologic changes were observed in the hearts of two of eight cats which had received 60 per cent of the minimal lethal dose. One cat died before sufficient time had elapsed for myocardial changes to occur.

3. When the dose of the drug was raised to 70 or 80 per cent of the minimal lethal dose, the frequency of cellular changes in the heart increased.

4. Regardless of the size of the single dose of drug, no definite myocardial lesions were seen during the first four days.

5. When histologic changes occurred after the administration of single doses of digitalis, they were almost always present between the fifth and the twelfth day.

6. Cellular changes in the heart were produced by digitalis whole leaf or by crystalline products of digitalis (digitoxin, lanatosides A, B, and C).

7. In not all of the animals which received toxic doses of digitalis did myocardial lesions develop, even when the duration of the experiment was five days or more (that is, within the period during which lesions are producible).

Although it is interesting to know the minimal amount of digitalis which will produce myocardial damage when the drug is given in a single dose, it is more important from the standpoint of clinical application to ascertain the minimal amount which will cause myocardial injury when the drug is administered daily over a certain period of time, as in treating patients. With this thought in mind, a series of cats was digitalized with 30 per cent of the minimal lethal dose and then subjected to estimated daily doses of digitalis within the toxic range. These daily doses were estimated in the manner previously described in this paper.

As has been stated, the daily administration of the equivalent of 1 or 2 cat units to digitalized animals for a period as long as two months did not result in definite cellular changes in the myocardium. Table IV summarizes the effects of daily administration of the equivalent of 3, 4, 5.5, or 6 cat units on the myocardiums of the digitalized animals, and the data indicate the following:

1. In five of seven digitalized cats which received the equivalent of 3 cat units daily, lesions developed in the myocardium. Digitoxin, given intravenously, produced lesions after five days, and digifortis (tincture of digitalis), administered orally, induced myocardial damage within eleven days.

2. Histologic changes were found in all of the digitalized cats which received the daily equivalent of 4, 5.5, or 6 cat units over periods varying from seven to thirty days.

(b) Remarks on the age of the animal with respect to the production of myocardial lesions. It is important to point out that the factor of age significantly altered the results of this study. The old animals

TABLE III
GROUP A₁

RELATION BETWEEN THE HISTOLOGIC FINDINGS IN THE MYOCARDIUM AND THE ADMINISTRATION OF A SINGLE TOXIC DOSE OF DIGITALIS

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES IN MYOCARDIUM				
				PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVEN-TRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
Digalen	40	Intravenous	12 days	No	No	No	No	No
Digluglusin	40	Intravenous	12 days	No	No	No	No	No
Lanatoside A	40	Intravenous	12 days	No	No	No	No	No
Lanatoside C	50	Intravenous	11 days	No	No	No	No	No
Digitoxin	50	Intravenous	13 days	No	No	No	No	No
Lanatoside A	50	Intravenous	14 days	No	No	No	No	No
Digalen	50	Intravenous	15 days	No	No	No	No	No
Digitoxin	60	Intravenous	12 hours	No	No	No	No	No
Lanatoside C	60	Intravenous	9 days	No	No	No	No	No
Lanatoside A	60	Intravenous	10 days	No	No	No	No	No
Digitoxin	60	Intravenous	10 days	Yes + + + +	Yes + + + +	Yes + + +	Yes + +	Yes + +
Lanatoside C	60	Intravenous	11 days	Yes + + + +	Yes + + + +	Yes + +	Yes +	Yes +
Digluglusin	60	Intravenous	12 days	No	No	No	No	No
Digalen	60	Intravenous	12 days	No	No	No	No	No
Digluglusin	60	Intravenous	14 days	No	No	No	No	No
Digalen	60	Intravenous	15 days	No	No	No	No	No
Lanatoside A	60	Intravenous	15 days	No	No	No	No	No
Digitoxin	70	Intravenous	4 days	No	No	No	No	No
Lanatoside C	70	Intravenous	11 days	No	No	No	No	No
Digluglusin	70	Intravenous	12 days	Yes + +	Yes + +	Yes + +	Yes +	Yes +
Digluglusin	75	Intravenous	3 days	No	No	No	No	No
Digluglusin	75	Intravenous	9 days	Yes + +	Yes + +	Yes +	No	No
Lanatoside A	75	Intravenous	12 days	Yes + + +	Yes + + +	Yes + +	Yes ±	Yes ±
Digluglusin	80	Intravenous	29 minutes	No	No	No	No	No
Lanatoside A	80	Intravenous	3 hours	No	No	No	No	No
Lanatoside A	80	Intravenous	4 hours	No	No	No	No	No

[illegible]

TABLE IV

RELATION BETWEEN THE HISTOLOGIC FINDINGS IN THE MYOCARDIUM AND THE DAILY ADMINISTRATION OF THE EQUIVALENT OF 3, 4, 5.5, OR 6 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED WITH 30 PER CENT OF THE MINIMAL LETHAL DOSE

GROUP B₁

DRUG USED	DAILY EQUIVALENT DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	HISTOLOGIC CHANGES IN MYOCARDIUM				
				PAPILLARY MUSCLE AND LEFT VENTRICLE	INTER-VENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
Digitoxin	3	Intravenous	5	Yes + + + + +	Yes + + + + +	Yes + + + +	Yes + + + +	Yes + + + +
Digitofortis	3	Oral	11	Yes + + + + +	Yes + + + + +	Yes + + + +	Yes + + + +	Yes + + + +
Tincture digitalis	3	Intravenous	13	Yes + + + + +	Yes + + + + +	Yes + + + +	Yes + + + +	Yes + + + +
Tincture digitalis	3	Intravenous	14	No	No	No	No	No
Tincture digitalis	3	Intravenous	18	No	No	No	No	No
Lanatoside A	3	Intravenous	25	Yes + + + +	Yes + + + +	Yes ±	No	No
Lanatoside A	3	Intravenous	30	Yes ±	Yes ±	No	No	No
Digiglusin	4	Intravenous	7	Yes + + +	Yes + + +	Yes ±	No	No
Digitofortis	4	Oral	14	Yes + + +	Yes + + +	No	No	No
Digitofortis	4	Oral	19	Yes + + ±	Yes + +	Yes +	No	No
Digitofortis	4	Oral	30	Yes +	Yes +	Yes ±	No	No
Lanatoside A	5.5	Intravenous	30	Yes + + + + +	Yes + + + + +	Yes + + + +	Yes + + + +	Yes + + + +
Digitofortis	6	Oral	30	Yes +	Yes ±	No	No	No

tolerated the digitalis bodies less well than the young ones, that is, the old animals were more prone to die after single or multiple doses of digitalis had been administered and more likely to show lesions in the myocardium, and these myocardial lesions were more likely to be extensive. For example, a young cat which received the daily equivalent of 6 cat units of digifortis (tincture of digitalis) for thirty days showed far less extensive lesions in the myocardium than did an old cat which received the daily equivalent of only 3 cat units of digifortis for eleven days.

(c) The myocardial histologic changes produced by toxic doses of digitalis. So far we have mentioned only the dosage of digitalis and the intervals in relation to the myocardial lesions. Let us now discuss the sequence of pathologic events in the development of these myocardial lesions. It must be kept in mind that the histologic changes were found only after administration of toxic doses of digitalis, and not after the administration of calculated therapeutic doses of this drug.

Among the early microscopic changes which were seen in the hearts of animals that had died spontaneously or had been killed within one to four days after single or multiple toxic doses of digitalis bodies were zones of capillary engorgement and regions of muscle which stained deeply with eosin and exhibited a more or less homogeneous appearance and coarse granulations in the perinuclear cytoplasm, or rather large clear spaces around the nuclei of the muscle fibers. None of these were considered sufficiently definite to justify classifying them as evidence of clear-cut histologic changes. When they occurred they were not counted in our results as myocardial lesions. This position was taken to minimize the inclusion of falsely positive observations.

Our anatomic studies confirm those of Levitski and Büchner. The earliest definite cellular change was a degeneration of the myocardial fibers. The latter seemed to vacuolate, fragment, and disintegrate in focalized zones of the myocardium (Fig. 1). Hemorrhage was often seen in the regions of degeneration of muscular fibers (Fig. 2). Later, exudative cells entered the region of degeneration (Fig. 3). These exudative cells included neutrophilic leucocytes, lymphocytes, and histiocytes. At this stage the lesions were typical of inflammation. As the degenerative and exudative components began to subside, the connective tissue cells (fibroblasts) proliferated (Fig. 4). If the administration of digitalis was discontinued and the dosage of the drug had not been too large these myocardial lesions began to heal. The degenerating material and the exudative cells were replaced gradually by fibroblasts. The recently healed lesions were composed of loosely interwoven fibroblasts (Fig. 5). These focalized scars were scattered throughout the myocardium. After a time these regions of scar tissue contracted, and it was sometimes difficult to locate them in the heart after six to eight weeks (unless the damage to the myocardium had been extensive).

As previous workers have pointed out, there was a predilection of these focalized lesions for certain regions of the myocardium. The



Fig. 1.—Early degeneration of the myocardial fibers after administration of a toxic dose of digitalis (X450).

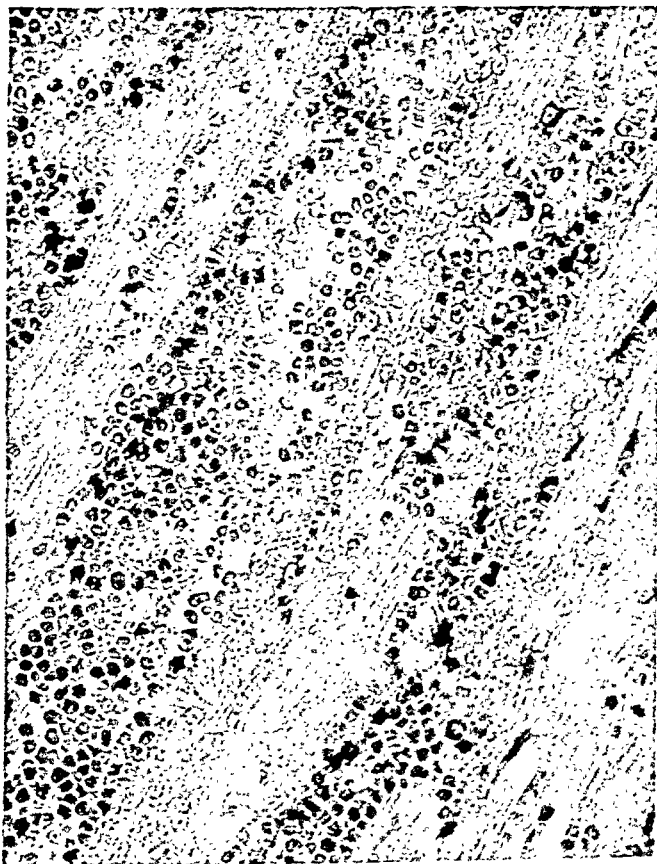


Fig. 2.—Hemorrhage into zones of degenerating myocardium after administration of a toxic dose of digitalis (X450).

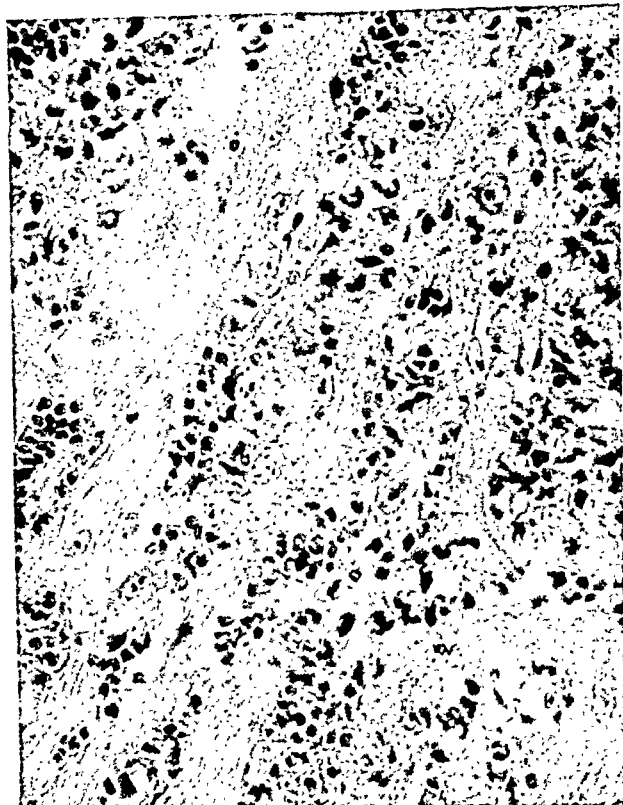


Fig. 3.—Degeneration of the myocardial fibers, plus numerous exudative cells after administration of a toxic dose of digitalis ($\times 450$).



Fig. 4.—Early signs of healing in myocardial lesion after administration of a toxic dose of digitalis. Fibroblasts are proliferating ($\times 450$).

anatomic changes were more likely to be found in the papillary muscle than anywhere else in the heart; next in frequency were the left ventricular wall and the interventricular septum. Histologic changes were observed in the right ventricular wall, but they were much less frequent and extensive than those in the left ventricular wall. Demonstrable cellular changes in the auricles and atria were seen in only a few animals.

There was perhaps a tendency for the histologic changes to be more frequent and more extensive in the subendocardial region of the myocardium than in other regions, but they were also often found throughout the entire depth of the ventricular wall, from the epicardium to the endocardium.

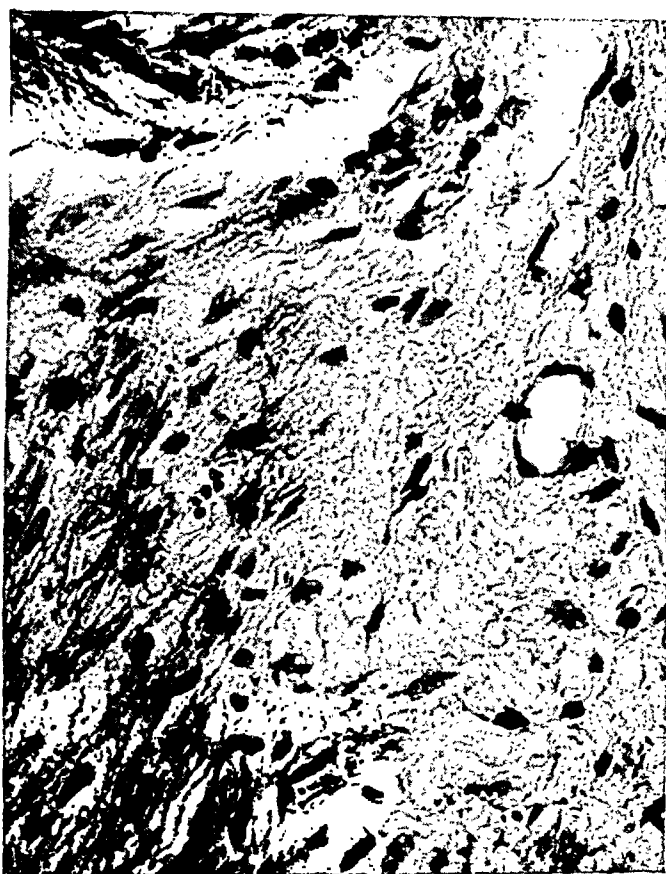


Fig. 5.—Recently healed myocardial lesion produced by digitalis. Fibroblasts have replaced the destroyed myocardial fibers ($\times 450$).

Before concluding our remarks on the histologic studies of the heart, it might be well to emphasize again that no evidence of any abnormality of the coronary arteries, including arteriosclerosis, was observed in any of the controls or the animals treated with digitalis.

D. Anatomic Studies of the Skeletal and Smooth Musculature of the Control Animals and of Those Treated With Digitalis.—One might ask whether toxic doses of digitalis which were capable of producing lesions in the cardiac muscle were able also to cause cellular changes

in the skeletal or smooth musculature of the experimental animals. Histologic study of the skeletal musculature (biceps, abdominal wall, and diaphragm) and the smooth musculature (stomach, duodenum, ileum, and uterus) in each of the control animals and in the animals which had received therapeutic or toxic doses of digitalis bodies failed to reveal any evidence of pathologic changes. These studies of the extracardiac musculature were made routinely on every animal used in these experiments.

E. Observations on Signs of Intoxication in the Cats Treated With Digitalis.—Vomiting for a few hours and anorexia for one day or so were observed in some of the animals which received calculated therapeutic doses of digitalis. No significant arrhythmias were noted after calculated therapeutic doses of digitalis. The cardiac rate in these animals was slowed, accelerated, or unchanged. In our experiments the cardiac rate was found not to be a reliable guide to the quantity of digitalis administered. A few days after a therapeutic dose of digitalis the appearance of the animals was not different from what it had been in the control period before digitalization.

The incidence of vomiting and anorexia was greater in the animals which received toxic doses of digitalis than in those which received therapeutic doses. Not all the animals vomited, even after 80 per cent of the minimal lethal dose had been administered. Loss of weight occurred in the severely intoxicated cats, and drowsiness was noted fairly frequently in these animals.¹³ Arrhythmias of various types occurred with toxic doses of the drug.¹² Many of the animals which were intoxicated with digitalis showed an accelerated heart rate instead of bradycardia. The latter, however, was observed commonly. Only a few of the animals exhibited the so-called anginal syndrome, as described by Büchner,³ after an intravenous injection of digitalis. These signs disappeared after a brief period.

Some of the animals which had been quite ill and had shown suggestive signs of myocardial injury in their electrocardiograms recovered completely. Their appetites returned to normal, they gained weight, the electrocardiograms resumed contours similar to those of the control periods, and, to all intents and purposes, the animals were normal. These animals had had myocardial lesions which healed.

F. Preliminary Observations on the Relation Between Dosage of Digitalis and Myocardial Lesions in Hyperthyroid Cats.—Hyperthyroidism was induced with thyroid extract or thyroxin in a series of cats. Extensive myocardial lesions were observed in some of the hyperthyroid animals which had received a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose). As has been shown, this dose of digitalis did not produce any demonstrable anatomic changes in the normal animal. Toxic doses of digitalis either killed the hyperthyroid animals promptly or caused extensive myocardial damage. These experimental results will be reported in a separate paper.

COMMENT

Discussion of Sources of Error in Our Experiments on Digitalis.—The bio-assay of the potency of digitalis leaves introduced an unavoidable source of error into our experiments. It is agreed by everyone that the bio-assay of digitalis is not entirely satisfactory; yet it is perhaps the most reliable method available at the present time. It was necessary for us to rely on bio-assay in order to ascertain the potency of our digitalis leaves, even though it was apparent to us that 0.1 Gm. of a given standardized preparation of digitalis leaves may be lethal for one cat which weighs 1 kg. and not for another cat of the same weight under identical experimental conditions. There is no known simple method of controlling the biologic variables which contribute to the production of differences of sensitivity to drugs among various individuals of the same species. Even when crystalline products of digitalis, which can be standardized gravimetrically, are used, the minimal lethal dose for the cat may vary considerably as a result of variations of individual sensitivity to the drug. Therefore, the size of the dose of any given preparation of digitalis which is required to produce a certain response in the cat is only an approximate value.

In our present state of knowledge, one is forced to use animals to assay the digitalis which is to be used in the treatment of patients. There is no assurance that man and animal are equally sensitive to digitalis. It is thought, however, that the sensitivity to digitalis of the cat is more like that of man than is the sensitivity of any other commonly used laboratory animal. Although experimentation in the future may indicate that the cat unit is not an adequate guide for the estimation of the dosage of digitalis in man, we have used this unit in our experiments to compare the dosage of digitalis in man and in the cat.

For the lack of a better method, we have assumed arbitrarily that, if a daily dose of 0.1 Gm. of a given preparation of digitalis is necessary to maintain digitalization in the case of a 70-kilogram man, a seventieth of 0.1 Gm., or 0.00143 Gm., will maintain digitalization in a cat which weighs 1 kg. This assumption is obviously open to criticism, but we are not aware of a better and simpler method of ascertaining for the cat the dose of digitalis which corresponds to 1 cat unit in man.

It should be kept in mind that these experiments on digitalis were done, to the best of our knowledge, on healthy cats that had normal myocardial structure and normal vascular systems. Myocardial and arterial diseases were not complicated factors in our animals.

It might be well to point out that our method of histologic study does not give information regarding the multitude of chemical and other changes which may occur in the myocardium before demonstrable morphologic changes are observable. The absence of myocardial lesions soon after the administration of toxic doses of digitalis does not mean that chemical changes in the myocardium, which may lead later to cellular necrosis, have not already occurred.

SUMMARY

No microscopic pathologic changes were found in the myocardiums or coronary arteries of the control animals.

No evidence of histologic changes was found in the myocardiums of the experimental animals after the administration of calculated therapeutic amounts of digitalis (30 per cent of minimal lethal dose) in single or divided doses, given over a period of forty-eight hours. The histologic studies were made after a minimum of six days and a maximum of fifty-six days.

Myocardial lesions were not produced in our experimental animals when they were digitalized rapidly with a calculated therapeutic dose of digitalis, and were then given daily maintenance doses of the drug which were estimated to correspond to either 1 or 2 cat units for a man weighing 70 kg. The histologic studies were made after a minimum of nineteen days and a maximum of sixty days.

In our experiments, 60 per cent of the minimal lethal dose was the smallest amount of digitalis which, when given as a single dose, produced definite evidence of myocardial lesions. This dose of digitalis is in the toxic range.

The frequency with which myocardial lesions occurred increased as the size of the single dose of digitalis was increased to 80 per cent of the minimal lethal dose.

Myocardial lesions were not found until five or more days after the single toxic doses of digitalis had been administered.

Histologic changes were not observed in the hearts of all the animals which had received toxic amounts of digitalis, even when the quantity of the drug was 80 per cent of the minimal lethal dose.

Histologic changes were produced in the myocardium when the animals were digitalized rapidly with a calculated therapeutic dose of digitalis, and were then given daily quantities of the drug which were estimated to correspond to 3, 4, 5.5, or 6 cat units for a man weighing 70 kg. The equivalent of 3 cat units daily of parenterally administered digitoxin caused myocardial lesions within five days in one animal, whereas the same amount of orally administered tincture of digitalis produced myocardial lesions within eleven days in another animal. The digitalized animals in this group which received daily doses of digitalis in the toxic range had their myocardiums examined microscopically after a minimum of five days and a maximum of thirty days.

Histologic changes in the heart were produced by digitalis whole leaf or by crystalline products of digitalis (digitoxin, lanatoside A, lanatoside B, and lanatoside C).

The sequence of pathologic changes in the myocardium after the administration of toxic doses of digitalis was studied. The observations of Levitski¹ and Büchner² were confirmed.

The myocardial lesions were focal in distribution, and were more frequent in the papillary muscles and in the left ventricular wall than

in other regions. This also confirmed the observations of Levitski and Büchner.

Animals which survived the toxic doses of digitalis recovered completely in three or more weeks. Animals which had myocardial scars produced by digitalis (healed lesions) appeared entirely normal after three to four or more weeks.

Myocardial lesions were more prone to develop in old animals after the administration of digitalis than in young ones. This difference in sensitivity to the drug was not related to arteriosclerosis, for no evidence of this disease was found in the cardiac arteries or arterioles of any of the cats.

Experimental hyperthyroidism increased the sensitivity of the animals to digitalis. Myocardial lesions were found after the administration of calculated therapeutic doses of digitalis to hyperthyroid cats.

No evidence of anatomic changes was seen in the skeletal musculature or the smooth musculature of any of the animals which had received digitalis in therapeutic or toxic quantities.

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EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

II. EFFECTS ON THE ELECTROCARDIOGRAM*

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THE purpose of this investigation was to ascertain whether characteristic electrocardiographic patterns accompany the myocardial lesions produced by digitalis, as described in a previous paper.¹

LITERATURE

Numerous investigators have described the effects of digitalis bodies on the electrocardiogram of man and animals. Nicolai and Simons² administered 3 Gm. of powdered digitalis leaves daily for five days to four human subjects and observed an increase in the amplitude of the T wave. Straub³ gave toxic doses of strophanthin (3 mg.) to anesthetized cats; he observed inversion or elevation of the T wave. Selenin⁴ observed in morphinized dogs an increase in the size of the T wave after the administration of digitoxin. Bickel and Tsvividis⁵ injected digitalysatum into rabbits and observed a slight decrease in the height of the T wave with moderate doses (1 c.c. per kilogram) and a decrease in height of the T wave with larger doses. Bickel and Pawlow⁶ came to a similar conclusion after administering small and large doses of strophanthin and digistrophan to dogs and rabbits. Rothberger and Winterberg⁷ did not observe any change in the electrocardiogram of the dog with small doses of strophanthin; large doses sometimes produced inversion of the T wave. Cohn, Fraser, and Jamieson⁸ concluded that digitalis (average of 0.4 Gm. daily) produced a lowering of the T wave, and later an inversion. They stated that the changes in the T wave developed as early as thirty-six to forty-eight hours and persisted as long as twenty-two days after the digitalis had been administered. White and Sattler⁹ considered a decrease in the amplitude of the T wave to be the earliest sign of the action of digitalis. They gave 2 to 3 Gm. of standardized digitalis over periods of seven to fourteen days to human subjects.

Robinson and Wilson¹⁰ reported negative T waves in cats which had received 10 per cent of the calculated minimal lethal dose of digitalis every ten minutes. The negative T wave appeared when approximately

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25 per cent of the minimal lethal dose had been administered. Harris and Edin¹¹ described a depression of the RS-T segment in the electrocardiograms of human subjects after the administration of 1 dram (3.7 c.c.) of digitalis a day for a fortnight. The depressed RS-T segment was regarded as a sign of digitalis intoxication. Pardee¹² reported electrocardiographic changes in man after giving 1 minim (0.06 c.c.) of standardized tincture of digitalis per pound (0.5 kg.) of body weight. The T wave in Lead III was first decreased in height and then inverted; these changes appeared two to four hours after the digitalis had been administered, reached a maximum in six to seven hours, and persisted for a period of twenty-four hours without change. Pardee¹³ tested forty-one persons with four different standardized tinctures of digitalis and concluded that the changes in the T wave could be used as a measure of the minimal effective dose. McCulloch and Rupe¹⁴ studied the effects of digitalis on the electrocardiograms of children. They stated that, with full digitalization, the changes were not constant in all cases. Marvin, Pastor, and Carmichael¹⁵ administered 1.5 Gm. of standardized digitalis per 10 pounds (4.5 kg.) of body weight and observed reversal of the T waves or depression of the RS-T segment in twenty-nine of thirty subjects.

DeGraff and Wible¹⁶ observed in cats an elevation of the RS-T segments after the administration of digitalis. They pointed out its similarity to the RS-T change which occurs soon after myocardial infarction. Yacoel and Papapanayotou¹⁷ reported that an increase in the height of the T waves accompanied improvement in the condition of patients who were receiving digitalis and ouabain. This is in contrast to the observations of Pardee. Cohn and Stewart¹⁸ observed changes in the direction of the T wave in dogs after the administration of therapeutic doses of digifoline (0.5 c.c. per kilogram). Kahlson¹⁹ observed an increase in the height of T waves in cases of heart disease and a decrease in their height in normal persons after the administration of digitalis. Brams²⁰ studied the effects on dogs and cats of various preparations of digitalis in therapeutic and toxic doses. Constant lowering of the T wave did not occur and in no case was a negative T wave observed. He doubted that changes in the T wave could be used as a criterion of the action of digitalis, as Pardee had suggested. The same conclusion was reached by Brams and Gaberman²¹ when they administered an average of 4.5 c.c. of digifoline to human subjects until nausea, vomiting, precordial distress, or heart block occurred. Schwartz and Weiss,²² Blumenfeldt and Strauss,²³ and Grünbaum²⁴ came to similar conclusions about the T wave after the administration of digitalis to human subjects. On the contrary, Bromer and Blumgart²⁵ regarded the T-wave changes as a quantitative index of the amount of digitalis in the body.

Larsen, Neukirch, and Nielsen²⁶ studied the effects of therapeutic doses of digitalis on fifteen young adults; in fourteen of these subjects

the T wave became lower in one or more leads. Herles²⁷ pointed out that changes in the RS-T segment and T wave occurred primarily in Leads I and II with left ventricular strain, and predominantly in Leads II and III with right ventricular strain. Winternitz²⁸ called attention to two types of changes in the RS-T segment after the administration of digitalis, namely a trough-shaped or bowl-shaped depression, and an oblique depression.

The foregoing review indicates the diversity of opinion regarding the nature of the electrocardiographic changes, and also regarding the interpretation of their significance, after the administration of any given dose of digitalis.

Several workers have published papers dealing with the problem in which we are primarily interested, namely, the relation between electrocardiographic changes and the myocardial damage produced by toxic doses of digitalis bodies. Bauer²⁹ studied the electrocardiograms on some of his cats. He intimated that the negative T wave was an indication of cardiac damage. Korth and Spang³⁰ observed depression or elevation of the RS-T segment in cats after the administration of toxic amounts of digitoxin in single or multiple doses; depression of the RS-T segment was not associated with myocardial necrosis, but elevation of the segment did constitute evidence of necrosis in the cardiac muscle. Spang and Korth³¹ amplified their previous studies to emphasize their observation that depression of the RS-T segment does not indicate the presence of myocardial lesions. Baur and Reindell³² studied the tracings from cats which received digitoxin in small and in large doses (0.025 to 0.1 mg. per kilogram). They described ten different electrocardiographic changes, and stated that the patterns after the administration of small doses of digitalis (unassociated with cardiac lesions) may be the same as those after the administration of large doses (associated with myocardial necrosis). It is not quite clear which patterns were indicative of myocardial damage.

METHODS

With a few exceptions, the electrocardiographic studies with digitalis were made on the same cats which were used in the previously described experiments¹ dealing with anatomic changes in the myocardium.

A Sanborn portable cardiette served to record the electrocardiograms. The machine was standardized carefully at the beginning of each lead. A deflection of 1 cm. represented a potential difference of 1 millivolt. The three conventional leads were used in all experiments (Lead I, right foreleg and left foreleg; Lead II, right foreleg and left hindleg; Lead III, left foreleg and left hindleg).

Small areas were shaved on the proper extremities for the attachment of the lead wires. A commercial electrode paste was used to insure good contact between the electrodes and the skin of the animal. As a further precaution, gauze was placed between the two forelegs and between the two hindlegs to prevent contact of the extremities while the electrocardiograms were being made.

Each animal was trained to lie quietly on its right side on a table over which a rubberized cushion had been placed. During this period of training, electro-

cardiograms were made daily. When the animal was trained satisfactorily and the electrocardiograms had attained a fairly constant contour (which persisted for several days), digitalis was administered.

It is not necessary to repeat the names of the various preparations of digitalis, their dosage, methods of administration, and so forth, for they were the same as described in the paper¹ dealing with the anatomic studies on the myocardium.

RESULTS

It is planned to attempt to correlate the dosage of digitalis, the electrocardiographic changes, and the anatomic studies on the myocardium.

A. Electrocardiographic Studies of the Control Animals.—There was considerable variation of cardiac rate. Sinus arrhythmia was observed frequently. The T wave in Lead III was often negative. A slight elevation of the RS-T segment was seen in some of the control animals and in some of the experimental animals during the control period (before administration of digitalis).

The histologic studies of the myocardium of the control animals failed to reveal any evidence of structural disease.

B. Electrocardiographic Studies of Animals Which Received Therapeutic Doses of Digitalis.—In order to simplify the presentation of the studies correlating the electrocardiographic changes with the dosage of digitalis and the histologic investigations of the myocardium, the experimental animals were divided into two groups: (1) Group A, those which received the calculated therapeutic amount of digitalis (20 or 30 per cent of the minimal lethal dose) in a single dose within an interval of two to three minutes, or in divided doses over a period of forty-eight hours; (2) Group B, those which received the calculated therapeutic amount of digitalis in a single digitalizing dose, and, thereafter, daily maintenance quantities of the drug over a period of nineteen to sixty days. The daily maintenance doses were calculated as indicated in a previous paper;¹ they were the estimated equivalent of either 1 or 2 cat units per day (a 70-kilogram man and the body weight of each cat were used as the basis for these calculations).

In both Group A and Group B, electrocardiograms were taken, as a rule, six hours after the drug had been administered, and then once or twice daily throughout the duration of the experiment.

In Group A there were thirteen cats (Table I). No anatomic changes in the myocardium were observed, and the electrocardiographic alterations were not constant. Studies of the RS-T segments and T waves in approximately 250 electrocardiograms (each with three leads) revealed the following: (1) no significant change; (2) positive T_3 changed to negative T_3 ; (3) negative T_3 changed to positive T_3 ; (4) decrease of height of T wave in one or more leads; (5) increase of height of T wave in one or more leads.

There were slight increases or decreases in the height of the T waves in the majority of the animals which received calculated therapeutic doses of digitalis, but the changes recorded in Table I are only those

TABLE I

CORRELATION OF THERAPEUTIC DOSE OF DIGITALIS, DURATION OF THE EXPERIMENT, AND THE MOST PROMINENT CHANGE IN THE RS-T SEGMENT AND T WAVE, GROUP A

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Lanatoside A	20	Single dose, intravenous	14	Increase in height of T_1 , T_2 , T_3
Digalen	20	Single dose	15	No significant changes
Digalen	30	Single dose	6	No significant changes
Lanatoside C	30	Single dose	11	Slight decrease in height of T_2
Digitoxin	30	Single dose	11	Decrease in height of T_1 ; negative T_2 became positive
Lanatoside A	30	Single dose	12	Decrease in height of T_1 for 24 hr.; then increase in height of T_1 , T_2 , and T_3
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12	Negative T_2 became positive
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12	Negative T_2
Digalen	30	Single dose, intravenous	14	Increase in height of T_1 , T_2 , T_3
Digitoxin	30	Single dose, intravenous	14	Decrease in height of T_1 and negative T_2
Lanatoside A	30	Single dose, intravenous	18	No significant change
Lanatoside A	30	Single dose, intravenous	21	Negative T_2
Digifortis	30	Single dose, oral	56	Slight decrease in height of T_1 and T_2 for a few days

which were more or less prominent. Significant elevation or depression of the RS-T segment was not observed in any of the animals in Group A.

In Group B there were eleven cats (Table II). In these animals, which received a therapeutic dose of digitalis, plus estimated daily maintenance quantities of the drug, there were likewise no demonstrable myocardial lesions and no consistently typical electrocardiographic changes. Studies of the RS-T segments and T waves in approximately 350 electrocardiograms (each with three leads) revealed the following: (1) no significant change; (2) positive T_3 changed to negative T_3 ; (3) negative T_3 changed to positive T_3 ; (4) decrease of height of T waves in one or more leads; (5) increase of height of T waves in one or more leads.

In both Groups A and B, changes of cardiac rhythm were observed (no significant change, tachycardia, or bradycardia), but they were difficult to evaluate. Under the conditions of our experiments, even with the well-trained cats, cardiac rate did not seem to be a reliable index to the quantity of drug which the animal had received.

TABLE II

CORRELATION BETWEEN DOSAGE OF DIGITALIS, DURATION OF THE EXPERIMENT, AND MOST PROMINENT CHANGE IN RS-T SEGMENT AND T WAVE

The animals were digitalized with a calculated therapeutic dose of digitalis (30 per cent of minimal lethal dose), and then given a daily dose of digitalis to correspond to either 1 or 2 cat units daily for a man weighing 70 kg.

GROUP B

DRUG USED	EQUIVALENT DAILY MAIN- TENANCE DOSE, CAT UNITS	METHOD OF ADMINISTRA- TION	DURATION OF EXPERIMENT, DAYS	MOST PROMINENT RS-T AND T CHANGE OBSERVED
Digalen	1	Intravenous	19	No significant change
Digifortis	1	Oral	19	Negative T ₂ became positive
Digifortis	1	Oral	30	No significant change
Digalen	1	Intravenous	34	Negative T ₂
Lanatoside A	1	Intravenous	36	No significant change
Digiglusin	2	Intravenous	20	Negative T ₂ ; decrease in height of T ₁
Digifortis	2	Oral	30	No significant change
Digalen	2	Intravenous	30	Tall T waves
Lanatoside A	2	Intravenous	36	Negative T ₂
Digalen	2	Intravenous	40	Negative T ₂
Digifortis	2	Oral	60	No significant change

Sinus arrhythmia, prolongation of the P-R interval, and shortening of the Q-T interval were observed in some of the animals. No ventricular premature contractions were noted in any of the electrocardiograms of the animals in Group A or Group B.

All of the electrocardiographic changes in Group A and Group B were reversible. The changes in the RS-T segment and T wave listed in Tables I and II constitute the predominant alteration during the period of observation. For example, in one case a negative T₂ developed six hours after 30 per cent of the minimal lethal dose of digitalis had been injected; this electrocardiographic change persisted for a few days and then disappeared.

C. Electrocardiographic Studies of Animals Which Received Toxic Doses of Digitalis.—It is difficult to group the animals in this series of experiments, for the dosage of digitalis and the intervals varied considerably. For convenience in presentation, the animals were arranged in two major groups: (1) Group A₁, those animals which received a single toxic dose of digitalis, had daily electrocardiograms (tracings were often made at hourly intervals on the day the drug was administered), and finally had the myocardium examined microscopically after varying periods; (2) Group B₁, those animals which received multiple doses of digitalis in various amounts over different periods, had daily electrocardiograms, and ultimately had their hearts subjected to histologic study.

Before the data are presented on these two major groups of animals, it might be well to point out again that in this section of the paper

TABLE III

CORRELATION OF SINGLE TOXIC DOSES OF DIGITALIS, DURATION OF THE EXPERIMENT, HISTOLOGIC STUDIES OF MYOCARDIUM, AND THE MOST PROMINENT CHANGES IN RS-T SEGMENT AND T WAVE

The changes in the RS-T segment and T wave are the most prominent which were observed during the course of the experiment; they do not represent the only change which occurred, or, necessarily, the final change. Many of the tracings returned to the control contour before the experiment was terminated.

GROUP A₁

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRA- TION	DURATION OF EXPERI- MENT	HISTO- LOGIC CHANGE IN MYO- CARDIUM	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Digalen	40	Intravenous	12 days	No	Negative T ₂ ; decrease in height of T ₁ and T ₂
Digiglusin	40	Intravenous	12 days	No	Negative T ₂
Lanatoside A	40	Intravenous	12 days	No	Negative T ₂ ; decrease in height of T ₁ and T ₂
Lanatoside C	50	Intravenous	11 days	No	Negative T ₂
Digitoxin	50	Intravenous	13 days	No	Negative T ₂ ; decreased height of T ₁ and T ₂ ; later, increased height of T ₁ , T ₂ , and T ₃
Lanatoside A	50	Intravenous	14 days	No	Negative T ₂
Digalen	50	Intravenous	15 days	No	Decreased height of all T waves, and then negative T ₂
Digitoxin	60	Intravenous	12 hrs.	No	Decreased height of T ₁ , T ₂ , and T ₃
Lanatoside C	60	Intravenous	9 days	No	
Lanatoside A	60	Intravenous	10 days	No	No significant change
Digitoxin	60	Intravenous	10 days	Yes	Elevation of RS-T ₁ , RS-T ₂ , and RS-T ₃
Lanatoside C	60	Intravenous	11 days	Yes	No significant change
Digiglusin	60	Intravenous	12 days	No	Depression of RS-T ₂ and RS-T ₃
Digalen	60	Intravenous	14 days	No	Negative T ₂
Digalen	60	Intravenous	15 days	No	Negative T ₂
Lanatoside A	60	Intravenous	15 days	No	Negative T ₂ ; depression of RS-T ₁ and RS-T ₂
Digitoxin	70	Intravenous	4 days	No	Depression of RS-T ₁ , RS-T ₂ , and RS-T ₃
Lanatoside C	70	Intravenous	11 days	No	No significant change
Digiglusin	70	Intravenous	12 days	Yes	Depression of RS-T ₁ , RS-T ₂ , and RS-T ₃ and then elevation of RS-T ₁ and RS-T ₂
Digiglusin	75	Intravenous	3 days	No	Slight elevation of RS-T ₁ , RS-T ₂ , and RS-T ₃
Digiglusin	75	Intravenous	9 days	Yes	Negative T ₂ ; elevation of RS-T ₁ and RS-T ₂
Lanatoside A	75	Intravenous	12 days	Yes	
Digiglusin	80	Intravenous	39 min.	No	Died, ventricular fibrillation

(Table continued on next page.)

TABLE III—CONT'D

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRA- TION	DURATION OF EXPERI- MENT	HISTO- LOGIC CHANGE IN MYO- CARDIUM	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Lanatoside A	80	Intravenous	3 hrs.	No	Died, ventricular fibrillation
Lanatoside A	80	Intravenous	4 hrs.	No	Died, ventricular fibrillation
Lanatoside A	80	Intravenous	6½ hrs.	No	
Digalen	80	Intravenous	1 day	No	
Lanatoside A	80	Intravenous	2 days	No	Depression of RS-T, and RS-T ₂
Lanatoside A	80	Intravenous	3 days	No	Increased height of T ₂ and T ₃
Digalen	80	Intravenous	4 days	No	No significant change
Lanatoside A	80	Intravenous	5 days	Yes	Cove-plane, negative T ₂ and T ₃
Digitoxin	80	Intravenous	6 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Lanatoside A	80	Intravenous	7 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Lanatoside A	80	Intravenous	8 days	Yes	Elevation of RS-T ₁ and RS-T ₂ ; negative T ₂ be- came positive
Lanatoside C	80	Intravenous	9 days	No	No significant changes
Lanatoside A	80	Intravenous	10 days	No	Decreased height of T ₁ , T ₂ , and T ₃ ; slight de- pression of RS-T ₁
Lanatoside A	80	Intravenous	10 days	Yes	Negative T ₃ ; only few tracings
Lanatoside C	80	Intravenous	11 days	No	Elevation of RS-T ₂ and RS-T ₃ (not of plateau type)
Lanatoside A	80	Intravenous	12 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Digalen	80	Intravenous	12 days	Yes	Decreased height of T ₁ ; T ₂ became posi- tive; cove-plane, nega- tive T ₁ , and positive T ₂
Digiglusin	80	Intravenous	12 days	No	Striking depression of RS-T ₁ , RS-T ₂ and RS-T ₃
Lanatoside B	80	Intravenous	12 days	Yes	
Digitoxin	80	Intravenous	12 days	No	Increased height of T ₁ , T ₂ , and T ₃
Tincture digitalis	80	Intravenous	12 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Digifortis	80	Oral	13 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Lanatoside A	80	Intravenous	14 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Digalen	80	Intravenous	14 days	Yes	Elevation of RS-T ₁ , RS-T ₂ , and RS-T ₃

TABLE III—CONT'D

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRA- TION	DURATION OF EXPERI- MENT	HISTO- LOGIC CHANGE IN MYO- CARDIUM	MOST PROMINENT CHANGES OBSERVED IN RS-T AND T
Lanatoside A	80	Intravenous	16 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Digalen	80	Intravenous	17 days	Yes	Cove-plane, negative T ₂ and T ₃ ; diphasic T ₁
Lanatoside A	80	Intravenous	21 days	No	Negative T ₂
Lanatoside A	80	Intravenous	23 days	Yes	Elevation of RS-T ₁ and RS-T ₂ ; negative T ₂ became positive
Digalen	80	Intravenous	24 days	Yes	Elevation of RS-T ₁ and RS-T ₂
Digalen	80	Intravenous	30 days	Yes	Cove-plane, negative T ₂ and T ₃ ; positive T ₁
Lanatoside A	80	Intravenous	30 days	Yes	Elevation of RS-T ₁ and RS-T ₂ ; normal electrocardiogram when killed
Digalen	80	Intravenous	42 days	Yes	Depression of RS-T ₁ , RS-T ₂ , and RS-T ₃ ; then elevation of RS-T ₁ and RS-T ₂
Digalen	80	Intravenous	60 days	No	Negative T ₂

we are dealing with toxic doses of digitalis and not with so-called therapeutic doses.

Table III summarizes the observations on the animals of Group A₁. The following are the various changes in the RS-T segments and T waves (Fig. 1) in more than 900 electrocardiograms (each with three leads) after different toxic amounts of digitalis had been administered as single doses: (1) no significant change; (2) positive T₃ changed to negative T₃; (3) decrease in height of T wave in one or more leads; (4) increase in height of T wave in one or more leads; (5) depression of the RS-T segment in one or more leads (6) cove-plane, negative T₂ and T₃, with positive or diphasic T₁; (7) cove-plane, negative T₁ and positive T₂ and T₃; (8) elevation of RS-T₁ and RS-T₂; (9) elevation of RS-T₂ and RS-T₃; (10) elevation of RS-T segment in all leads.

The following is an analysis of each of these electrocardiographic patterns in relation to the presence or absence of histologic changes in the myocardium.

Myocardial lesions were not found, as a rule, when there were no significant changes in the electrocardiograms. However, in one case myocardial lesions were present, but daily electrocardiograms failed to show any abnormality.

When a negative T₃ or a change in the height of the T wave constituted the only significant electrocardiographic abnormality, there was no demonstrable evidence of morphologic change in the myocardium.

The familiar depression of the RS-T segment (Figs. 1*f* and *g* and 2) in one or more leads was not associated with demonstrable histologic changes. If, however, this pattern was replaced by one in which the RS-T segment was elevated in two or more leads, myocardial lesions were observed.

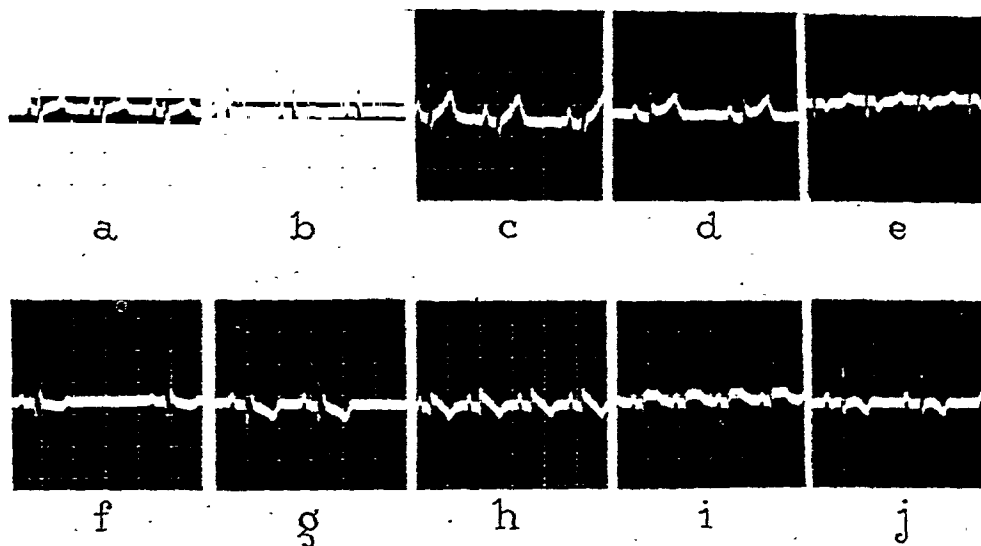


Fig. 1.—Electrocardiograms (all Lead II) selected to show the various types of changes which were observed after administration of toxic doses of digitalis: *a*, control; *b*, decrease in height of T wave (one or more leads); *c*, increase in height of T wave (one or more leads); *d*, slight elevation of RS-T segment (one or more leads); *e*, simple inversion of T wave (one or more leads, usually in Lead III); *f*, bowl-type of depression of the RS-T segment (one or more leads); *g*, angulated type of depression of RS-T segment (one or more leads); *h*, initial portion of RS-T segment above isoelectric position and terminal portion below isoelectric line; transition between *g* and *i* (one or more leads); *i*, plateau type of elevation of RS-T segment (one or more leads); *j*, cove-plane, negative T wave (Leads I and II or Leads II and III).

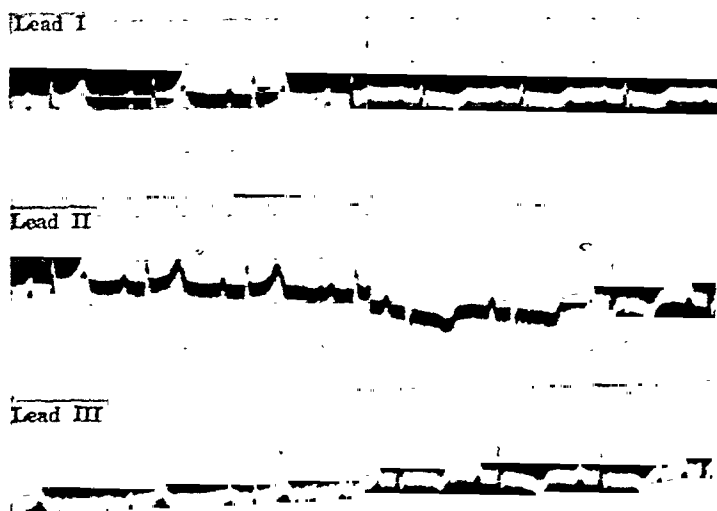


Fig. 2.—On the left, control electrocardiogram; on the right, depression of the RS-T segment after administration of a toxic dose of digitalis. Myocardial lesions were not associated with this pattern.

We observed several electrocardiographic patterns which were usually associated with myocardial histologic changes. The following is a list of these patterns: (1) elevation of RS-T₁ and RS-T₂; (2) elevation of RS-T₂ and RS-T₃; (3) elevation of RS-T₁, RS-T₂, and RS-T₃; (4) positive T₁ and cove-plane, negative T₂ and T₃; (5) cove-plane, negative T₁ and positive T₂ and T₃.

It is important to point out that the elevation of the RS-T segment must show certain characteristics if the foregoing statement is to be valid. Elevation of the segment must persist one to three days, and the segment must take off high on the R wave, pass along more or less horizontally, and then grade into the T wave, almost completely obliterating the ascending limb of the latter (Figs. 1i and 3). If the elevated segment exhibited a high take-off from the R wave but was followed by a distinct ascending limb of the T wave (Fig. 1d), myocardial lesions were seldom found; this pattern is usually transitory, and, in some cases, may be associated with metabolic changes in the myocardium which, if they persisted long enough, could be precursors of anatomic changes.^{1, 33}

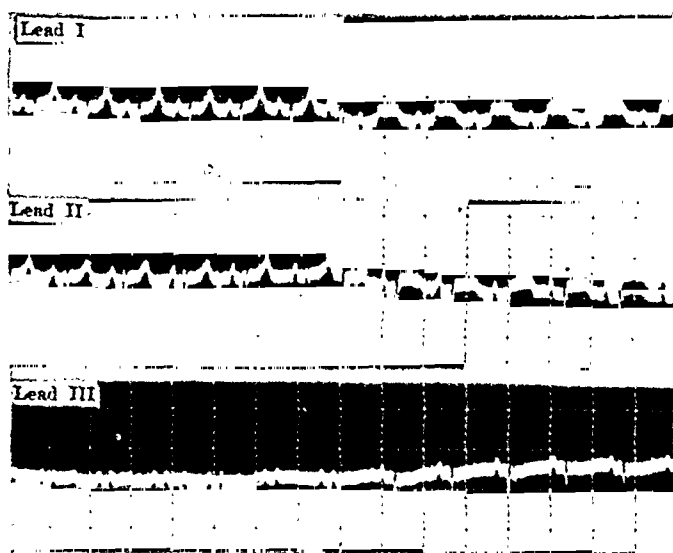


Fig. 3.—On the left, control electrocardiogram; on the right, "plateau type" of elevation of RS-T₁ and RS-T₂. Myocardial lesions were associated with this pattern.

Although, in these experiments, simple negativity of T₃ was not accompanied by myocardial lesions, cove-plane negativity of T₂ and T₃ was usually associated with histologic changes in the myocardium (Fig. 4). Again, this pattern must persist one to three days to make this statement valid.

The cove-plane, negative T₁ and positive T₃ pattern was observed definitely only once, and occurred in an animal which had histologic lesions in the myocardium.

One might wonder whether elevation of the RS-T segment in all leads was associated with acute exudative pericarditis. Animals in which this electrocardiographic pattern was observed did not show any gross signs of pericarditis. Subepicardial lesions might account for the electrocardiographic changes but specific investigations were not made to answer this question with certainty.

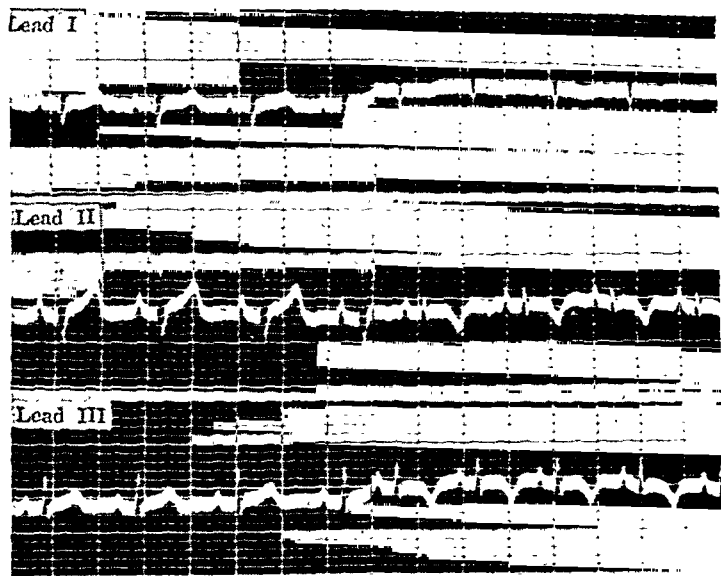


Fig. 4.—On the left, control electrocardiogram; on the right, cove-plane, negative T_2 and T_3 . Myocardial lesions were associated with this pattern.

It should be emphasized that the changes in the RS-T segment and T wave recorded in Table III represent the most prominent alterations that were observed in the series of daily electrocardiograms on each animal. The contents of the table were simplified by eliminating comments on changes which were perhaps of minor importance for the solution of our problem (sinus tachycardia, sinus bradycardia, sinus arrhythmia, partial and complete heart block, ventricular premature contractions, coupling of beats, ventricular tachycardia, ventricular fibrillation, changes in the height and direction of the P wave, changes in the QRS complex, minor changes in the height of the T-wave, and changes in the P-R and Q-T intervals). It could not be shown that these electrocardiographic alterations gave any clues to the presence or absence of demonstrable morphologic changes in the myocardium. A toxic dose of digitalis may produce all or any one of the foregoing changes within the course of a few hours, and even cause the death of the animal; yet no demonstrable myocardial lesions can be found. On the contrary, these electrocardiographic changes may be observed at various times during the course of daily observations on animals which have received toxic doses of digitalis. For example, complete heart block or ventricular fibrillation may develop one hour after the administration of a single toxic dose of digitalis, but there may not be

any demonstrable anatomic changes in the myocardium, or these two disturbances of rhythm may develop ten days after a single toxic dose of digitalis and there may be ample histologic evidence of changes in the myocardium. Therefore, it was necessary to rely on changes in the RS-T segment and T wave, rather than on any of the numerous electrocardiographic alterations listed in the former part of this paragraph, to give us hints about the histologic status of the myocardium after the administration of toxic doses of digitalis.

Before concluding our remarks on the electrocardiographic alterations produced by digitalis, it is of interest that the changes in the RS-T segment and T wave indicated in Table III did not persist indefinitely. The electrocardiogram frequently was observed to have returned to normal in those animals which were killed approximately between the tenth and twentieth day after the toxic dose of digitalis had been administered, although histologic evidence of inflammation was still present in the myocardial lesions, in which fibroblastic proliferation was beginning. Furthermore, the electrocardiogram had become entirely normal in all the animals in which the myocardial lesions were shown by microscopic examination to have healed.

The time of observation after the administration of any given toxic dose of digitalis is important in correlating the electrocardiographic changes with the histologic structure of the myocardium. A study of the limited amount of data included in Table III indicates the significance of this interval. If the animal had received a given toxic dose of digitalis and had been killed (or had died spontaneously) before sufficient time had elapsed for demonstrable histologic changes to develop, the electrocardiographic observations were different from those on animals which had been permitted to survive long enough for myocardial lesions to develop. Furthermore, if the interval was selected properly, the electrocardiogram might have returned to normal, although healing lesions, with active inflammatory components, were present in the myocardium. Finally, if the tracings were taken during the stage in which myocardial scars were present, the electrocardiogram was normal and there was no evidence in the tracing that the myocardium was filled with focalized zones of fibrosis.

Now let us turn to a consideration of the electrocardiographic changes in Group B₁, that is, in those animals which were digitalized with calculated therapeutic amounts of digitalis and then were given daily doses of digitalis in the estimated toxic range (daily doses to correspond to 3.4, 5.5, or 6 cat units; the body weight of the cat, in kilograms, and the weight of a 70-kilogram man were taken as the basis for these calculations). Group B₁ (Table IV) was composed of thirteen cats on which more than 250 electrocardiograms (each with three leads) were made. As in the foregoing Group A₁, it was found that elevation of the RS-T segments and cove-plane, negative T waves in Leads II and III were associated with myocardial lesions when these electrocardiographic

changes persisted one to several days. Depression of the RS-T segment was unassociated with myocardial lesions.

TABLE IV

CORRELATION OF DOSAGE OF DIGITALIS, DURATION OF THE EXPERIMENT, HISTOLOGIC STUDIES OF THE MYOCARDIUM, AND THE MOST PROMINENT CHANGES IN THE RS-T SEGMENT AND T WAVE

The animals were digitalized with a therapeutic dose (30 per cent of minimal lethal dose), and were then given daily quantities of digitalis estimated to correspond to 3, 4, 5.5, and 6 cat units daily for a man weighing 70 kg.

GROUP B₁

DRUG USED	EQUIVALENT DAILY MAINTENANCE DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	HISTOLOGIC CHANGES IN HEART	MOST PROMINENT CHANGE OBSERVED IN RS-T AND T
Digitoxin	3	Intravenous	5	Yes	Elevation of RS-T ₂ and RS-T ₃
Digifortis	3	Oral	11	Yes	Elevation of RS-T ₁ , RS-T ₂ , RS-T ₃
Tincture digitalis	3	Intravenous	13	Yes	Elevation of RS-T ₁ and RS-T ₃
Tincture digitalis	3	Intravenous	14	No	Depression of RS-T ₁ , RS-T ₂ , RS-T ₃
Tincture digitalis	3	Intravenous	18	No	Very slight elevation of RS-T ₁ and RS-T ₂
Lanatoside A	3	Intravenous	25	Yes	Elevation of RS-T ₂ and RS-T ₃
Lanatoside A	3	Intravenous	30	Yes	Elevation of RS-T ₁ and RS-T ₃
Digiglusin	4	Intravenous	7	Yes	Cove-plane, negative T ₂ and T ₃
Digifortis	4	Oral	14	Yes	Initial elevation and final depression of each RS-T segment in all leads
Digifortis	4	Oral	19	Yes	No significant change
Digifortis	4	Oral	30	Yes	Insufficient number of tracings
Lanatoside A	5.5	Intravenous	30	Yes	Cove-plane, negative T ₂ and T ₃
Digifortis	6	Oral	30	Yes	Elevation of RS-T ₂ and RS-T ₃

In one case, on the day on which the animal was killed the electrocardiogram showed an initial elevation and a terminal depression of each RS-T segment. That is, the segment began well above the isoelectric position and terminated well below it (Fig. 1*h*). This pattern was present in all leads. The myocardium of this animal was found to have recent degenerative lesions. This electrocardiographic pattern was observed several times in animals in group A₁; it represents a transitional stage between the depressed RS-T segment type (Fig. 1*g*) and the elevated RS-T segment type (Fig. 1*i*).

One animal in Group B₁ was found to have histologic changes in the myocardium, but no significant alterations were observed in any of the daily electrocardiograms.

COMMENT

The remarks made in the preceding paper¹ regarding the sources of error in the dosage of digitalis apply, of course, to these studies on the electrocardiographic changes after various amounts of the drug had been administered.

The electrocardiographic changes were variable, and there was a tendency for the tracing to revert to normal. It is likely that we may have missed some of the significant changes, for we made our electrocardiograms only once a day in the more prolonged experiments.

It should be kept in mind that the electrocardiographic changes which were described as indications of myocardial lesions were produced by doses of digitalis that were definitely toxic.

It should be pointed out that the electrocardiogram may be normal even though healing lesions, with histologic evidence of active inflammation, still persist in the heart. Therefore, the time at which the tracing is made is important.

The position of the animal must be defined if the electrocardiographic changes are to mean anything. For example, an animal treated with digitalis may have an elevated RS-T segment in Lead I and an isoelectric RS-T segment in Lead III while it lies on its right side, but these changes are reversed if the animal lies on its left side; that is, the RS-T segment becomes isoelectric in Lead I and elevated in Lead III.

Care was taken to avoid the technical errors which would result from incorrect standardization and poor contact between the animal's skin and the electrodes.

SUMMARY

Calculated therapeutic amounts (20 or 30 per cent of minimal lethal dose) of digitalis, in single doses, or in divided doses over a period of forty-eight hours, produced the following types of RS-T segment and T-wave changes: (1) No significant change; (2) positive T₂ changed to negative T₂; (3) negative T₂ changed to positive T₂; (4) decrease of height of T wave in one or more leads; (5) increase of height of T wave in one or more leads.

Similar electrocardiographic patterns were noted when animals were digitalized rapidly with a calculated therapeutic dose of digitalis and then were given daily doses which were estimated to be equivalent to 1 or 2 cat units a day for a 70-kilogram man. The electrocardiographic studies were made during experiments which lasted from six to fifty-six days.

Myocardial lesions were not observed in any of these two groups of animals.

In our experiments there were no constant changes in the RS-T segment or T wave which could be taken as a reliable index to the presence of a calculated therapeutic amount of digitalis. The cardiac rate was also unreliable; a therapeutic dose of digitalis produced an increase, decrease, or no change in the cardiac rate over a period of days.

Toxic amounts of digitalis, when administered in single doses (40 to 80 per cent of the minimal lethal dose), or when given daily to digitalized animals in an amount which corresponded to 3,4, 5.5, or 6 cat units for a 70-kilogram man, produced the following electrocardiographic alterations: (1) no significant change; (2) positive T_3 changed to negative T_3 ; (3) decrease of height of T wave in one or more leads; (4) increase of height of T wave in one or more leads; (5) depression of the RS-T segment in one or more leads; (6) change in the RS-T segment, the initial portion of which began above the isoelectric position and the terminal portion of which ended below the isoelectric line; (7) elevation of the RS-T segment ("plateau type") in one or more leads; (8) cove-plane, negative T_2 and T_3 , with positive T_1 ; (9) cove-plane, negative T_1 and positive T_2 and T_3 .

Changes (1) to (5), inclusive, were usually not associated with myocardial lesions, whereas patterns (6) to (9) were associated with myocardial lesions produced by digitalis.

Two animals that had microscopic evidence of myocardial lesions failed to show any significant changes in the daily electrocardiograms.

The electrocardiogram returned to normal in all animals which did not die spontaneously or were not killed for experimental reasons.

The electrocardiograms returned to normal while microscopic evidence of active inflammation persisted in the myocardium.

The electrocardiogram was normal in those animals in which the myocardial lesions had healed (focalized zones of fibrosis).

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THE VASOCONSTRICTOR AND ANGIOTONIN-NEUTRALIZING PROPERTIES OF RENAL VENOUS PLASMA

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INTRODUCTION

HOUSSAY and Taquini,^{1, 2} using the L wen-Trendelenburg perfusion technique in the toad, demonstrated that the venous blood from the ischemic kidneys of dogs rendered hypertensive by constriction of the renal arteries contained a strong vasoconstrictor substance which was not present in the plasma obtained from venous blood of normal kidneys or in the plasma from systemic blood. Blood plasma from other organs to which the arterial supply had been partially reduced did not contain such a vasoconstrictor substance. Taquini^{3, 4} and Prinzmetal and his associates⁵ also found a marked vasoconstrictor or pressor substance in the venous blood from kidneys which had been completely ischemic for five to seven hours.

Numerous investigators⁶⁻¹⁰ have demonstrated that acute constriction of the renal artery of a few minutes' duration is sufficient to produce a pressor substance in the venous blood of previously normal kidneys. Page and Helmer¹¹ were able to isolate a crystalline substance (angiotonin) from the interaction of renin and blood plasma which they believed was the effective pressor agent in the blood of hypertensive animals. Braun-Men ndez and his associates⁹ have also described a pressor substance which appears to be identical with angiotonin. These investigators discovered also that this pressor substance could be neutralized by normal blood plasma. It was later found¹² that this neutralizing effect was diminished in blood from a kidney in which the arterial flow and pressure had been greatly reduced, as compared with that of blood from a systemic artery.

In the present communication we report the results of a study of the venous blood plasma from kidneys in which the arterial pressure and flow had been markedly reduced with respect to (1) its vasoconstrictor properties and (2) its content of angiotonin neutralizer.

METHODS

The L wen-Trendelenburg perfusion technique was employed, using the California toad, *Bufo boreas kalophilus*, as the test animal. Briefly, the method consisted of perfusing a toad under constant pressure, first with Ringer's solution

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containing 0.5 per cent sodium citrate, and then with the test solution, the basic portion of which was also Ringer's solution containing 0.5 per cent citrate. The toad was perfused with the control Ringer's solution until a constant perfusion rate was obtained, and then the test solution was allowed to run into the preparation. The drops flowing from the toad preparation during the control and the test period were counted. The decrease in the number of drops during perfusion with test solution, divided by the rate of the control perfusate, was recorded, and this percentage figure was used to express the activity or relative potency of the test substance as a vasoconstrictor.

Blood was collected from a kidney in which the arterial blood pressure and blood flow were markedly reduced, at a rate of 5 to 10 c.c. per minute over a fifteen- to thirty-minute period, from normal, anesthetized (pentobarbital sodium), heparinized dogs by a method previously described.¹⁰ The blood flow through the kidney in these experiments was reduced approximately 90 to 95 per cent, and the renal arterial pressure was also markedly reduced. For control purposes, blood was also obtained from the brachial or jugular veins, and from the renal veins of normal kidneys. In all instances heparin was used as the anticoagulant, and the plasma obtained by centrifugation was then diluted with Ringer's solution containing 0.5 per cent citrate.

The following abbreviations will be used in the ensuing text to designate the various types of plasma:

1. D.K.P.—Venous blood plasma from a kidney in which arterial pressure and blood flow were markedly reduced.
2. N.K.P.—Venous blood plasma from a normal kidney.
3. N.V.P.—Normal, systemic, venous blood plasma.

TABLE I
THE VASOCONSTRICTOR EFFECT OF N.V.P. AND D.K.P.

EXP. NO.	CHANGE IN RATE OF OUTFLOW (PER CENT)	
	PERFUSION WITH D.K.P. (12.5 c.c.)*	PERFUSION WITH N.V.P. (12.5 c.c.)*
1	-50	-63
2	-76	+19
3		-18
4	-79	
5	-80	-39
6	-74	
7	-64	
8	-80	
9	-36	-33
10	-66	- 6
11	-60	
12	-80	-11
13		-11
14	-77	-29
15	-76	-20
Av.	-69	-26

*Diluted with Ringer's solution to 100 c.c.

RESULTS

A.—*The Vasoconstrictor Effect of D.K.P.*—Thirteen different samples of D.K.P. were diluted with Ringer's solution in the ratio of 12.5 c.c. of D.K.P. to 87.5 c.c. of Ringer's, or 1 part of D.K.P. to 8 parts of the total solution. When these D.K.P.-Ringer solutions were tested on the L wen-Trendelenburg toad preparation (See Table I), employing a

fifteen-minute perfusion period, an average decrease of 69 per cent in rate of outflow was observed. Ten different samples of normal, systemic, venous blood plasma (N.V.P.), similarly diluted with Ringer's solution and perfused through the L  wen-Trendelenburg toad preparation, caused an average decrease in rate of flow of only 26 per cent. It is concluded, therefore, that D.K.P. possesses a significantly greater vasoconstrictor effect than does N.K.P.

B.—*The Angiotonin Neutralizing Content of D.K.P.*—In a previous report,¹² the limited ability of D.K.P. to neutralize the pressor property of angiotonin, as compared with that of normal, systemic, arterial blood plasma, was noted. It was thought desirable, also, to ascertain whether D.K.P. was similarly deficient in ability to neutralize the vasoconstrictor property of angiotonin, as compared with N.K.P. For this purpose, angiotonin* solution, as well as samples of D.K.P. and N.K.P. from thirteen normal dogs, was obtained, and the following mixtures were prepared:

1. 0.025 c.c. angiotonin (control).
2. 0.5 c.c. D.K.P. (control).
3. 0.025 c.c. angiotonin plus 0.5 c.c. of D.K.P.
4. 0.025 c.c. angiotonin plus 0.5 c.c. of N.K.P.
5. 0.025 c.c. angiotonin plus 0.2 c.c. of D.K.P.
6. 0.025 c.c. angiotonin plus 0.2 c.c. of N.K.P.

These mixtures were incubated for one hour at 38° C., then diluted to 100 c.c. in Ringer's solution containing 0.5 per cent citrate, and perfused through the L  wen-Trendelenburg toad preparation for a five-minute period.

TABLE II

THE NEUTRALIZATION OF ANGIOTONIN BY N.K.P. AND D.K.P.

EXP. NO.	CHANGE IN RATE OF OUTFLOW (PER CENT)					
	PERFUSION WITH ANGIOTONIN (0.025 c.c.)*	PERFUSION WITH D.K.P. (0.5 c.c.)*	PERFUSION WITH N.K.P. (0.5 c.c.) PLUS ANGIOTONIN (0.025 c.c.)*	PERFUSION WITH D.K.P. (0.5 c.c.) PLUS ANGIOTONIN (0.025 c.c.)*	PERFUSION WITH N.K.P. (0.2 c.c.) PLUS ANGIOTONIN (0.025 c.c.)*	PERFUSION WITH D.K.P. (0.2 c.c.) PLUS ANGIOTONIN (0.025 c.c.)*
1b	-73	-23	+ 4	- 9	-23	-49
2b	-66	+ 6	-26	-49	-38	-67
3b	-76	- 9	-21	-54	-21	-55
4b	-70	- 3	- 7	-21	-40	-49
5b	-61	- 3	-14	-44	-28	-44
6b	-70		- 5	-34	-23	-52
7b			- 8	-48	+ 2	-28
8b			+ 8	-23	-21	-34
9b			+ 2	-28	-13	-19
10b			- 5	-19	-21	-49
11b			-15	-41	-26	-24
12b			- 2	-20	- 8	-34
13b			- 8	-22		
Av.	-69	- 6	- 7	-32	-22	-42

*Diluted with Ringer's solution to 100 c.c.

*We are indebted to Irvine H. Page for the angiotonin solution used in these experiments.

Examination of the results (Table II) reveals that, whereas angiotonin alone, in the dilution used, effected an average decrease of 69 per cent in the rate of outflow from the Låwen-Trendelenburg preparation, the same quantity of angiotonin, first incubated with normal kidney blood plasma, lost almost all of its ability to affect the rate of outflow. However, the same quantity of angiotonin, if first incubated with D.K.P., still decreased the rate of outflow 32 per cent and 42 per cent, respectively, depending upon the quantity of D.K.P. used in the partial neutralization process. Obviously, therefore, D.K.P. did not neutralize the vasoconstrictor effect of angiotonin as well as did N.K.P.

SUMMARY

Our experiments showed that blood from a kidney in which the arterial flow and pressure had been markedly reduced possessed a greater vasoconstrictor effect and a lesser ability to neutralize angiotonin than did normal kidney blood.

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ACUTE RHEUMATIC FEVER AND VALVULAR DAMAGE

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IN A NUMBER of studies^{1, 2, 3} of rheumatic fever, it has been emphasized that the age of the patient at the onset of the disease, the number of attacks, and the character of the illness are important factors in the development of permanent valvular damage. The concept that factors inherent in the patient himself may be of equal or greater importance has received little attention. The present study is an attempt to evaluate the relative importance of the character of the disease, as opposed to the constitutional make-up of the patient, in determining the occurrence of permanent cardiac damage after rheumatic fever.

MATERIAL

The present analysis comprises two hundred fourteen patients with acute rheumatic fever who were admitted to the hospital during one or more attacks. After the acute attack, they were kept under observation in the outpatient department for a period of not less than four years, and for an average period of nine years. Most of them were examined personally for the final evaluation of their cardiac status. The observations were analyzed with regard to the occurrence or nonoccurrence of permanent cardiac damage in relation to the number and severity of attacks of rheumatic fever and the age at the time of the first attack. The latter was not considered in detail, but only in regard to puberty; the age of puberty was taken as thirteen years.

OBSERVATIONS

Ninety-nine patients, or 46 per cent, showed no clinical evidence of heart disease. Physical examination, the electrocardiogram, the teleroentgenogram, and fluoroscopic examination were taken into consideration in arriving at this conclusion. This group is an extension of that previously reported.⁴

One hundred two patients, or 48 per cent, showed evidence of permanent valvular damage; adequate follow-up data could not be obtained in thirteen cases (6 per cent).

In the group with heart disease and in the group without heart disease, rheumatic fever appeared in single or multiple attacks before, after, or before and after, puberty (Table I). The incidence of permanent cardiac damage after multiple attacks was not higher than after single attacks in either the prepuberty or the postpuberty groups. Although the average age of the patients without heart disease (14.7 years) was slightly higher than that of those with heart disease (14.0

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years), an analysis of Table I, in relation to puberty, reveals that advancing age was no bar to either recurrences of rheumatic fever or the development of heart disease, and that the incidence of heart disease in the older group was the same as in the younger.

TABLE I
ACUTE RHEUMATIC FEVER
214 CASES

ONSET	NO HEART DISEASE		HEART DISEASE		NO FOLLOW-UP	
	NO.	%	NO.	%	NO.	%
Single attacks before puberty	30	14	11	5		
Multiple attacks before puberty	17	8	18	8		
Multiple attacks before and after puberty	11-	5	32	15		
Single attacks after puberty	29	14	22	10		
Multiple attacks after puberty	12	5	19	10		
Total	99	46	102	48	13	6

There were no discernible differences in the clinical characteristics of the rheumatic fever as far as the two groups were concerned. The severity and the duration of the disease, the electrocardiographic changes, and the incidence of pericarditis were similar.

Patients who show no permanent cardiac damage after the first attack of rheumatic fever are likely to escape permanent injury despite further attacks. Contrariwise, when patients developed heart disease, all of the valvular damage was evident after the first attack (Table II). The only relatively common exception was the late appearance of aortic stenosis.

TABLE II
APPEARANCE OF HEART DISEASE IN RELATION TO ATTACKS OF RHEUMATIC FEVER
102 CASES

	NUMBER OF CASES	PERCENTAGE
After first attack	52	51
At second attack	16	16
Before first known attack	18	17
Not known	16	16
Died of rheumatic fever, 11 patients		
Died of subacute bacterial endocarditis, 3 patients		

It is also to be noted that in the group with heart disease there were eleven deaths from acute rheumatic fever and three deaths from subacute bacterial endocarditis. No patient without evidence of valvular deformity died of acute rheumatic fever or bacterial endocarditis.

COMMENT

We have already called attention to the fact that the character of the rheumatic fever among the patients who recovered without permanent heart disease was no different from that among others. In this study we have shown that recurrences are equally frequent in both groups, and

do not bring about a higher incidence of heart disease. The age of the patient at the time of single or multiple attacks had nothing to do with the development of heart disease.

The fact that patients who show no permanent cardiac damage after the first attack of rheumatic fever are likely to escape it entirely has been observed before.^{4, 5} The apparent exception to this rule in the case of patients who develop aortic stenosis many years after an attack of rheumatic fever may be explained by the manner in which this lesion develops.

The fact that only patients with demonstrable valvular disease die of acute rheumatic fever or bacterial endocarditis is important prognostically, and has already been pointed out by others.⁶ It would thus appear that the life history of the disease is determined by the patient, and not by the severity, frequency, or character of the acute rheumatic attacks. It is impossible to state whether this represents an instance of specific resistance on the part of the heart, or whether there is a general immunologic reaction which alters the effect of rheumatic fever on the heart. It seems that the immunity of the host must play an important role, inasmuch as the patient who develops heart disease is the patient who may die of rheumatic fever, and the person who can resist the development of valvular damage does not die of rheumatic fever.

CONCLUSIONS

1. There is no relationship between the character of rheumatic fever, the number of recurrences, and the age of the patient at onset, on the one hand, and the development of cardiac damage, on the other hand.
2. Patients who develop valvular damage usually do so after the first attack of rheumatic fever.
3. The patient's immunity or resistance is the important factor in determining whether or not permanent valvular damage will develop.

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Clinical Reports

RECURRENT LARYNGEAL NERVE PALSY IN MITRAL STENOSIS

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RECURRENT laryngeal nerve palsy is a relatively uncommon complication of mitral stenosis. In spite of the very lucid anatomic explanation of this phenomenon by Fetterolf and Norris,¹ in 1911, there are still many who harbor the erroneous impression that the lesion is caused by direct compression by an enlarged left auricle. These authors demonstrated that the dilatation of the left auricle and pulmonary vessels which results from mitral stenosis causes a crowding of the mediastinal structures at the base of the heart. The dilated left superior pulmonary artery is literally pushed up against the nerve as it runs between this vessel and the aorta in the region of the ligamentum arteriosum. They made the additional observation that the function of the nerve was not always abolished by actual destruction from pressure, but that the same amount of functional disturbance might arise from a neuritis consequent upon a degree of compression not sufficient to destroy the vitality of the nerve. King and his collaborators,² in a very interesting paper, discussed recurrent laryngeal nerve palsy in cases of left ventricular failure and in the absence of mitral stenosis. They pointed out that failure of the left ventricle increases the pressure in the pulmonary circuit. This causes dilatation of the left superior pulmonary artery, which is responsible for compression of the nerve.

The following case re-emphasizes these points in dramatic fashion.

CASE REPORT

The patient was a 45-year-old Scotch woman; she was admitted to the Medical Service of Lincoln Hospital on Jan. 19, 1937, because of mildly active rheumatic heart disease. She gave a history of cardiac disease of ten years' duration, during which period she had noted increasing dyspnea on effort, and had experienced recurrent attacks of bronchitis and occasional hemoptysis. Three years earlier she had had a complete, right-sided hemiplegia, from which recovery was practically complete. In the preceding two years her voice had become increasingly hoarse, and this disability had been associated with dysphagia of moderate severity.

Physical examination revealed a poorly nourished woman who was slightly dyspneic and cyanotic. She was unable to speak above a whisper. There were indications of very marked enlargement of the heart. At the apex there was a rumbling presystolic murmur, and a blowing diastolic murmur was heard over the aortic area.

From the Medical Service of Lincoln Hospital, Bronx, N. Y.
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Fig. 1.—Teleoroentgenogram of chest, showing considerable enlargement of cardiac silhouette, with unusual prominence in region of pulmonic conus.



Fig. 2.—Left oblique anterior view, showing increased density of shadow cast by pulmonary artery beneath arch of aorta. The angle of bifurcation of the trachea remains unaltered, indicating absence of vertical enlargement of the left auricle.

The heartbeat was irregular. Residual evidence of the old hemiplegia consisted of exaggerated reflexes and ankle clonus on the right side. Examination of the larynx revealed adductor paralysis of the left vocal cord. Fluoroscopic and radiographic studies (Figs. 1, 2, 3) revealed pronounced enlargement in region of the outflow tract of the right ventricle, but no significant enlargement of the left auricle, either in a horizontal or vertical direction. The electrocardiogram showed marked right axis deviation and auricular fibrillation.

The patient had fever occasionally, usually associated with pain in the chest and exacerbation of the cough; these symptoms were variously interpreted as due to mild attacks of bronchopneumonia and pulmonary infarctions. After a prolonged stay in the hospital she was improved, and went home. However, she was compelled to return one week later because of increasing dyspnea and cough. This time her apparently favorable course was terminated rather suddenly by an acute pulmonary attack to which she succumbed.



Fig. 3.—Right oblique anterior view, showing the striking prominence of the pulmonic conus, and a barium-filled esophagus pursuing a relatively straight course, indicating no enlargement of the left auricle in a horizontal direction.

Autopsy.—The heart weighed 450 grams, and presented evidence of damage to both mitral and aortic leaflets. The mitral orifice showed marked stenosis. The left auricle was not much dilated, but the wall of this chamber showed distinct hypertrophy. The pulmonary artery and its major branches showed enormous dilatation. Both the main stem and the left branch exceeded the aorta in circumference. The left recurrent laryngeal nerve was found in its usual situation between the aorta and the left pulmonary artery. Grossly, it appeared normal, with no evidence of compression. Microscopic examination, however, revealed advanced myelin degeneration. The left vocal cord was atrophic. The lungs showed evidence of marked chronic passive congestion and were the seat of bronchopneumonia.

COMMENT

The syndrome of pulmonary hypertension resulting from mitral stenosis, which this patient had, is well known. The constant dyspnea, repeated attacks of bronchitis, pulmonary infarction, right axis deviation, and, finally, bronchopneumonia, are all clinical expressions of increased tension in the pulmonary circuit. Also, the enlargement of the left superior pulmonary artery, which causes the compression of the left recurrent laryngeal nerve, represents the effect of this hypertension on the lesser circulation. It is important to note that the left auricle was not demonstrably enlarged, and therefore could not have compressed the nerve. The reason for the failure of the auricle to dilate is not clear. Whatever the cause may be, it appears that the pulmonary vascular system compensated for it by excessive dilatation. Another feature of interest was the absence of gross evidence of compression of the nerve, although, microscopically, there was ample evidence of a degenerative change comparable to the so-called neuritis described by Fetterolf and Norris.¹

SUMMARY

A case of recurrent laryngeal nerve palsy complicating mitral stenosis is described; the nerve lesion was associated with marked pulmonary hypertension, which gave rise to considerable dilatation of the pulmonary artery and its major branches. The left auricle was not appreciably enlarged, and the suggestion is offered that the marked enlargement of the pulmonary vessels compensated for the failure of the auricle to dilate. Although there was no gross evidence of compression of the nerve, microscopic study revealed degenerative changes.

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PUNCTURE WOUND OF THE LEFT AURICLE, WITH TAMPONADE AND RECOVERY

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J. S., a white man, aged 34 years, became severely intoxicated on the evening of May 9, 1937, engaged in a street brawl, and was stabbed in the left side of the chest. A passing police patrol car picked him up and carried him to Rex Hospital. The chief surgeon of the hospital (Dr. Turner) was ready to perform another emergency operation. After seeing this patient in the accident ward and recognizing the seriousness of the situation, the other operation was delayed so that J. S. might have immediate attention. He was taken to the operating room and the operation was started with a minimum of preparation in order to conserve time.

At that time the patient was in shock and only semiconscious. His skin was cold and clammy and he was perspiring freely. His pulse was imperceptible, and his blood pressure could not be measured. The heart rate was so rapid that it could not be counted with a stethoscope. There were at least two stab wounds in the left side of the chest; one was over the seventh rib, and another was about an inch higher. Both were in the midclavicular line. A diagnosis of heart tamponade was made.

When he was put on the operating table, hypodermoclysis with physiologic saline was begun. He was given a hypodermic injection of $\frac{1}{4}$ grain of morphine and $\frac{1}{150}$ grain of atropine. The anesthetic was ether. During the operation 1000 c.c. of 10 per cent glucose in physiologic saline were given intravenously.

The incision was made at the site of the stab wounds, and the sixth and seventh left costal cartilages were resected. The tip of the knife blade was removed from the seventh left costal cartilage. The pericardium was exposed and incised. It was tightly filled with blood and blood clots. These were removed, and the stab wound, from which blood was spurting, was located on the lateral aspect of the left auricle. The auricular wound was closed with 20-day, chromic catgut. The pericardium was lightly irrigated with physiologic saline solution, and was closed with fine, chromic catgut. The left lung was collapsed, and there was a moderate amount of bloody fluid in the chest. The fluid was removed, two small, rubber-tube drains were inserted, and the chest wall was closed in routine manner. During the operation the pulse rate gradually fell to 120 per minute, and the pulse volume became good.

When he was returned to his room, the pulse rate was 120 per minute and his blood pressure was 52/40. Recovery from the anesthetic was satisfactory.

The following day his general condition was much better. His pulse rate remained at about 120 per minute, but the pulse volume was greatly improved. His blood pressure was 90/60. The heart sounds were faint. The drains were removed from the chest, and the opening was closed tightly. The following day his blood pressure was 105/60.

His postoperative rectal temperature was 104.2° F. There was a gradual fall in temperature until it reached normal on the tenth postoperative day. The temperature was slightly irregular for another week, but remained normal after that time. After the first week, his pulse rate ranged from 80 to 90 per minute. The respiratory rate was normal after the first week.

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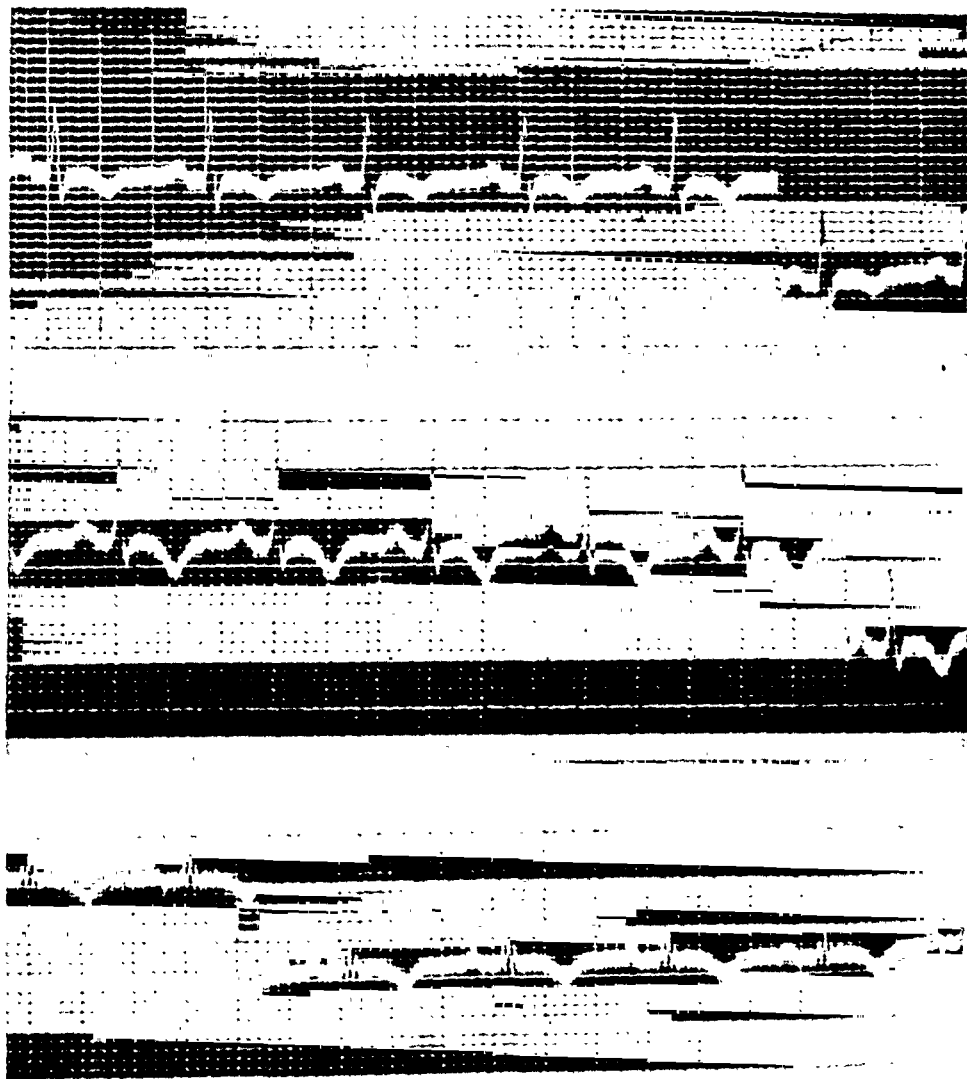


Fig. 1.—May 28, 1937; this tracing was made nineteen days after a puncture wound of the left auricle.

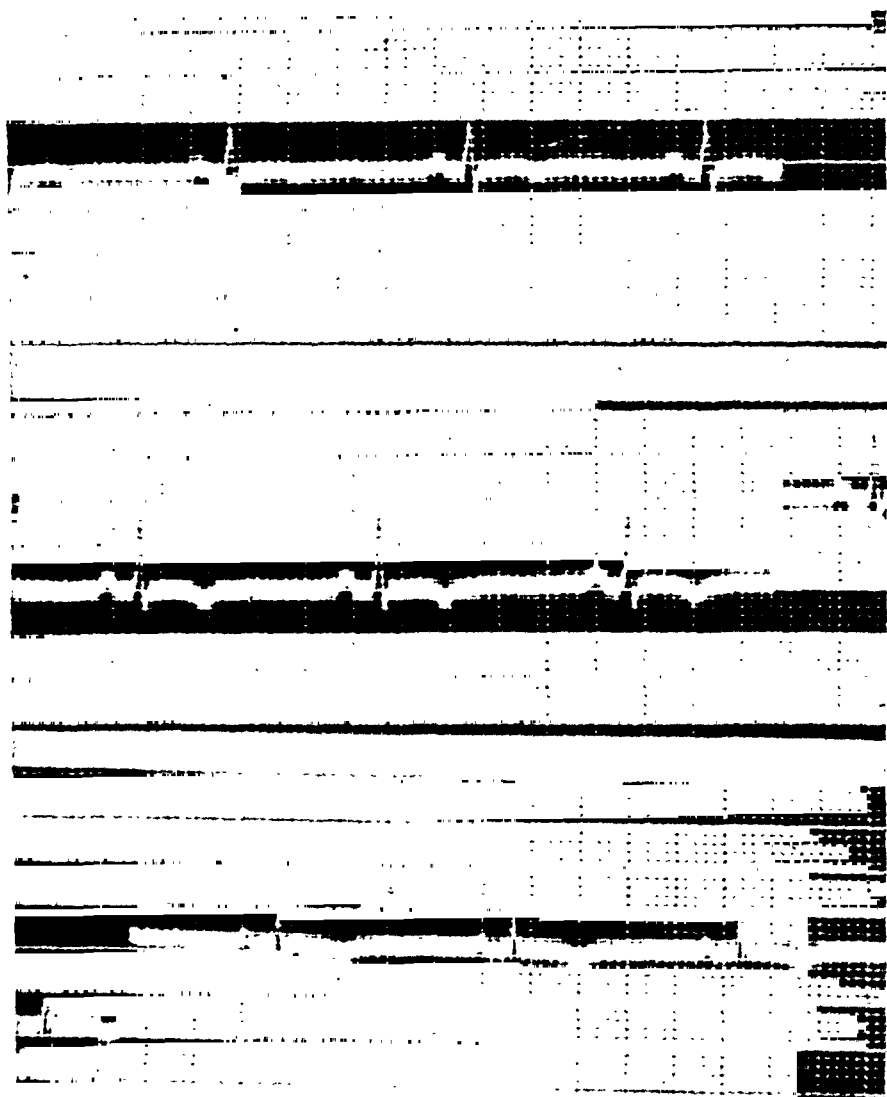


Fig. 2.—June 12, 1937.

The patient was never very anemic. During the first few weeks after the injury his hemoglobin was 70 per cent. Then it rose to 80 per cent, and has not changed appreciably since that time.

He appeared to have very little trouble on account of the collapsed left lung. A week after the injury, the left lung was generally hazy and there was slight pleural effusion. Two weeks later, the fluid was gone, and the lung was normal except for slight haziness over the base. After several weeks, the haziness in the base disappeared.

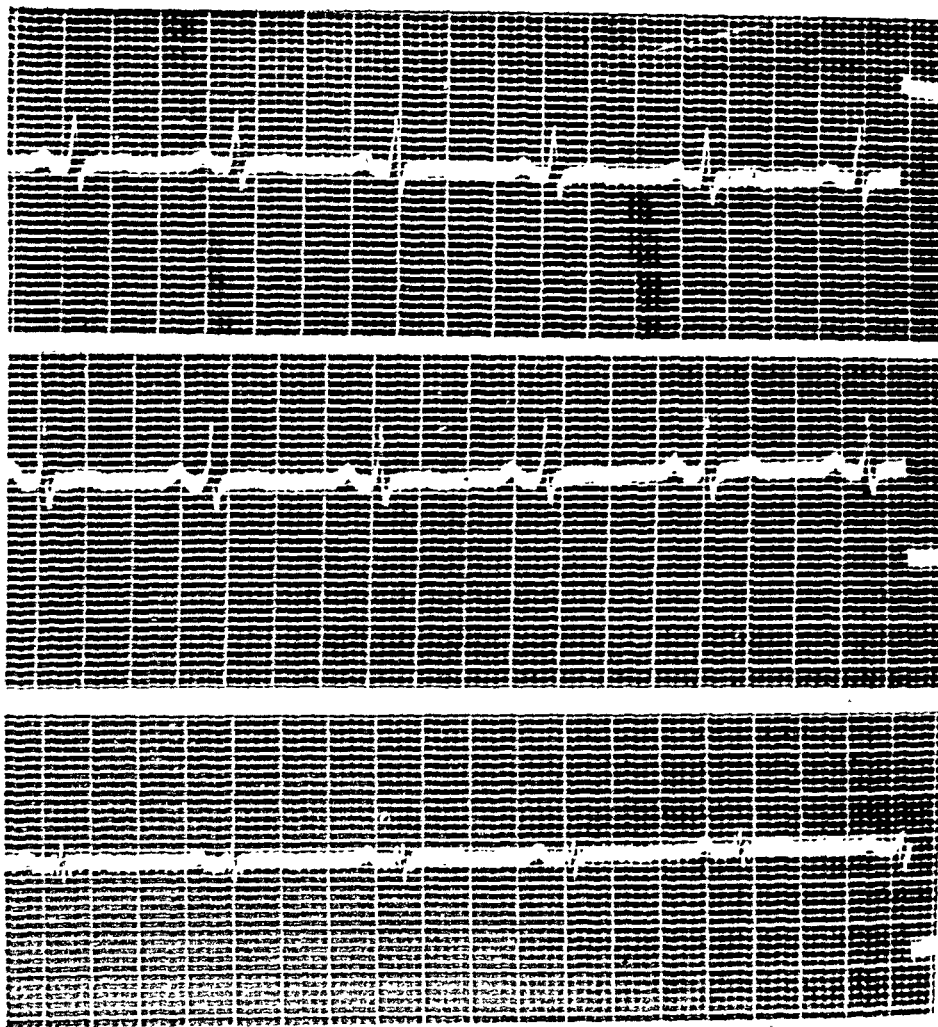


Fig. 3.—June 30, 1937.

When he was seen first by a medical consultant, May 28, 1937—nineteen days after the injury—the patient was quite ill. He was rather dusky in appearance, and had a rapid pulse and respiratory rate. His chest showed healing scars from the stab wounds and from the operation. There was a heaving precordial impulse, with intercostal retraction in systole. A thrill was felt at the apex in late diastole, and a rough murmur, beginning late in diastole and extending into systole, was heard at the apex. The apex beat was best heard and felt in the sixth left intercostal space, four inches to the left of the midsternal line. The heart rate was 100 per minute, and the heartbeat was regular and forceful; the sounds were generally roughened. The breath sounds were absent over the base of the left lung.

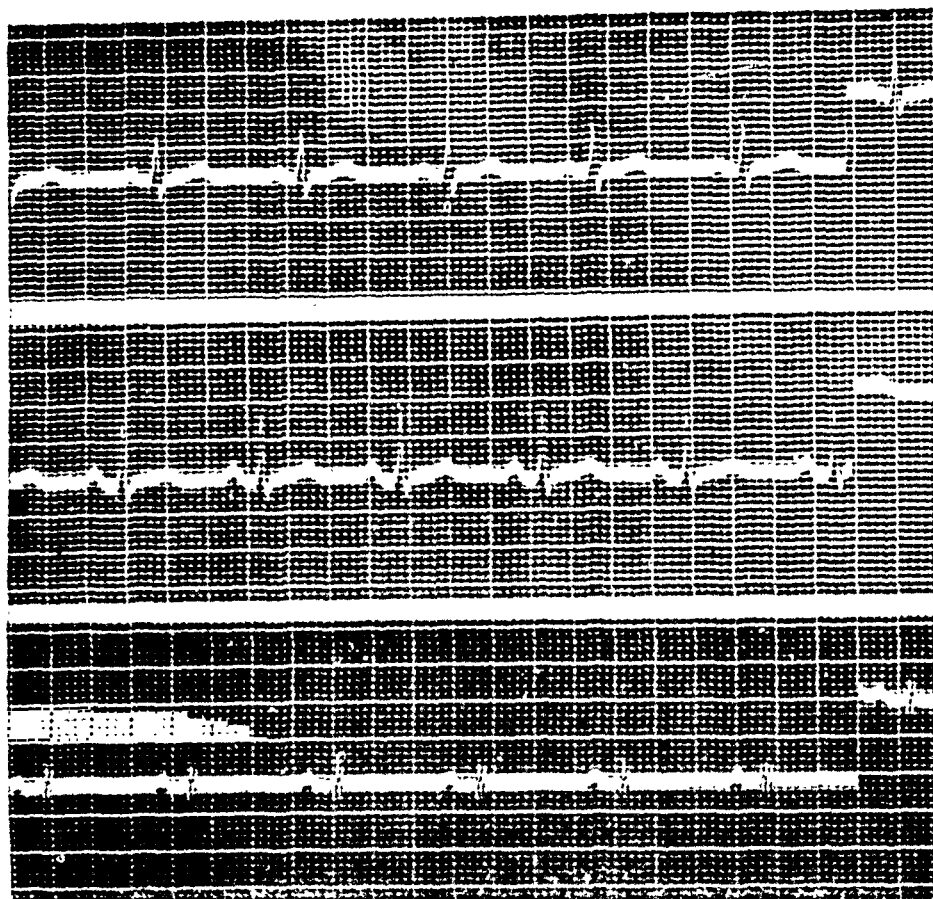


Fig. 4.—July 30, 1937.

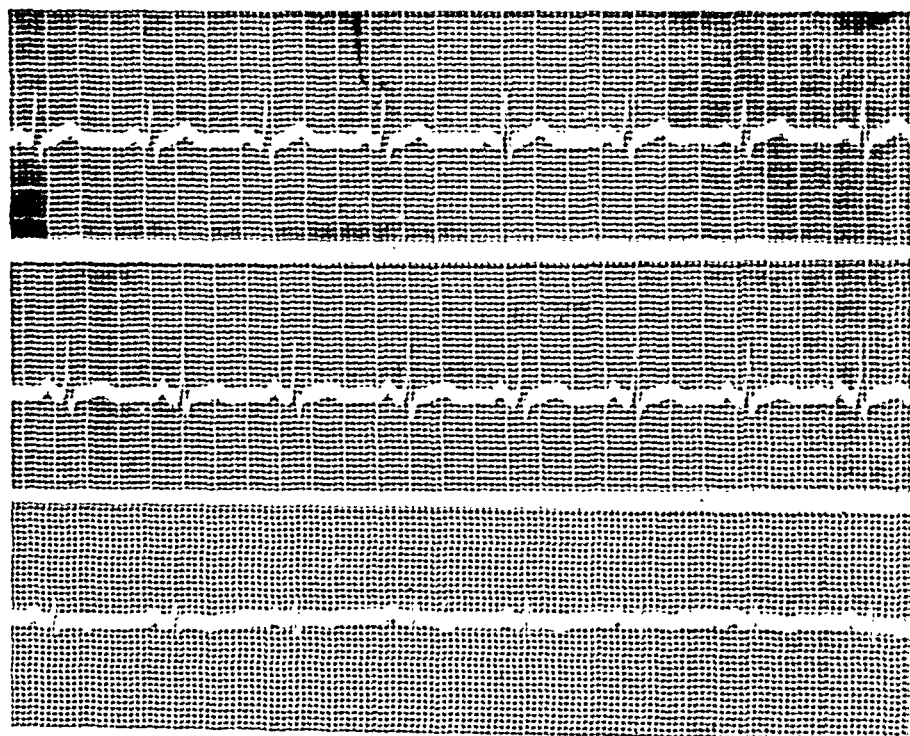


Fig. 5.—December 30, 1937.

The blood Wassermann reaction was negative. There was no history of syphilis or other serious illness. The patient had always been a laborer, and rarely ill. Physical examination showed nothing remarkable other than the injury.

The first electrocardiogram was made nineteen days after the injury (Fig. 1), and was like those which are often obtained after coronary occlusion. It showed normal rhythm, normal auriculoventricular conduction time (0.15 second), slight slurring of the QRS complexes, and negative T waves (Pardee type) in all leads. The P waves showed a slight diphasic tendency. The second tracing was made two weeks later, and showed a much slower rate and a definite return toward normal of the T waves in all leads (Fig. 2). There was no change in the P waves.

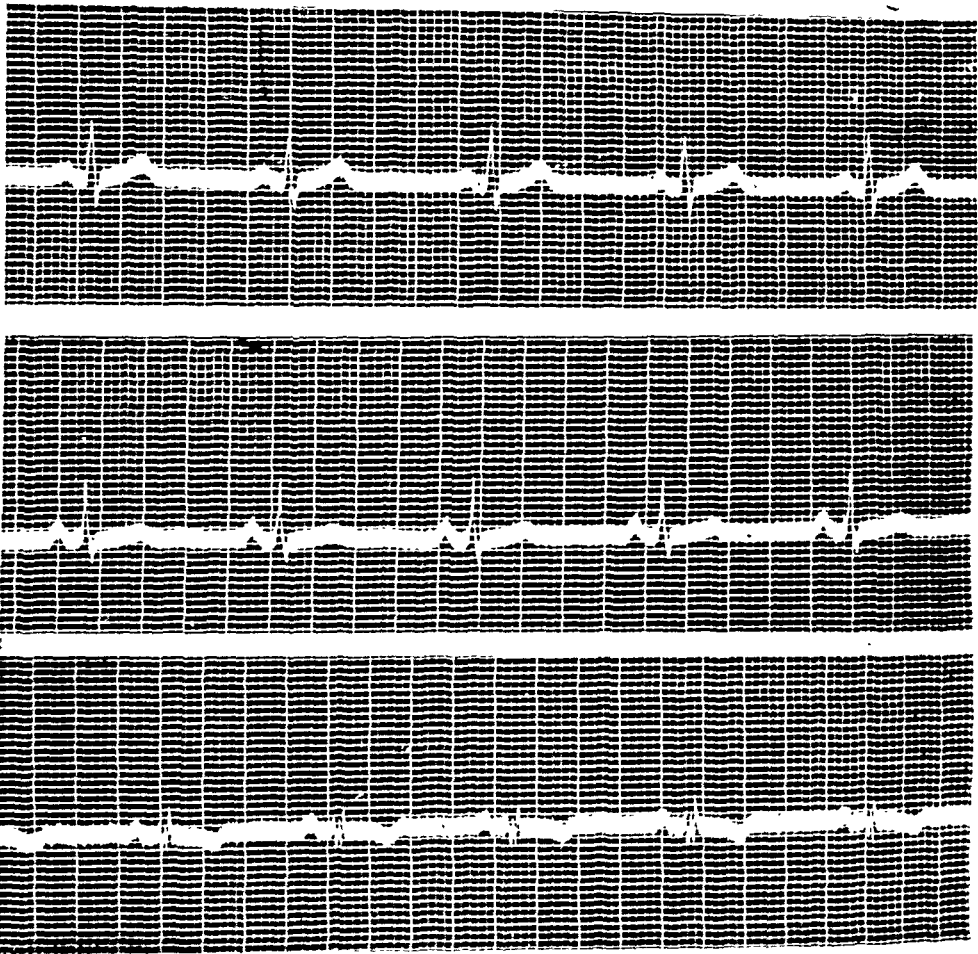


Fig. 6.—May 30, 1938.

Eighteen days later the tracing was almost normal in appearance, except for rather low amplitude of the T waves and some slurring of the QRS complexes (Fig. 3). There was still no change in the P waves. In tracings made a month later (Fig. 4), there was fair amplitude of the T waves in Leads I and II; in Lead III the T waves were almost isoelectric. The P waves were beginning to show improvement: in Lead I they were normal, and in Leads II and III they descended slightly lower after the upward thrust than before. In the later tracings (Figs. 5, 6, 7), as the patient's general condition improved, it will be noted that there was no change in the P waves, and that the diphasic tendency of P_2 and P_3 was still present; this tendency was observed in Lead IV. Also, T_2 became definitely negative.

During the first year after the injury, this man worked as a metal grader in a junk yard. This was heavy work, and at times he complained of dyspnea. Since

that time, except for periodic alcoholic debauches, he has been able to work regularly at anything he wished to do.

His blood pressure at the last reading was 144/90. That appears to be approximately his average pressure. His pulse rate has persistently remained in the eighties. The cardiac thrill and mitral murmurs have persisted; this suggests that he has an old rheumatic heart disease which was doubtless present before the injury occurred.

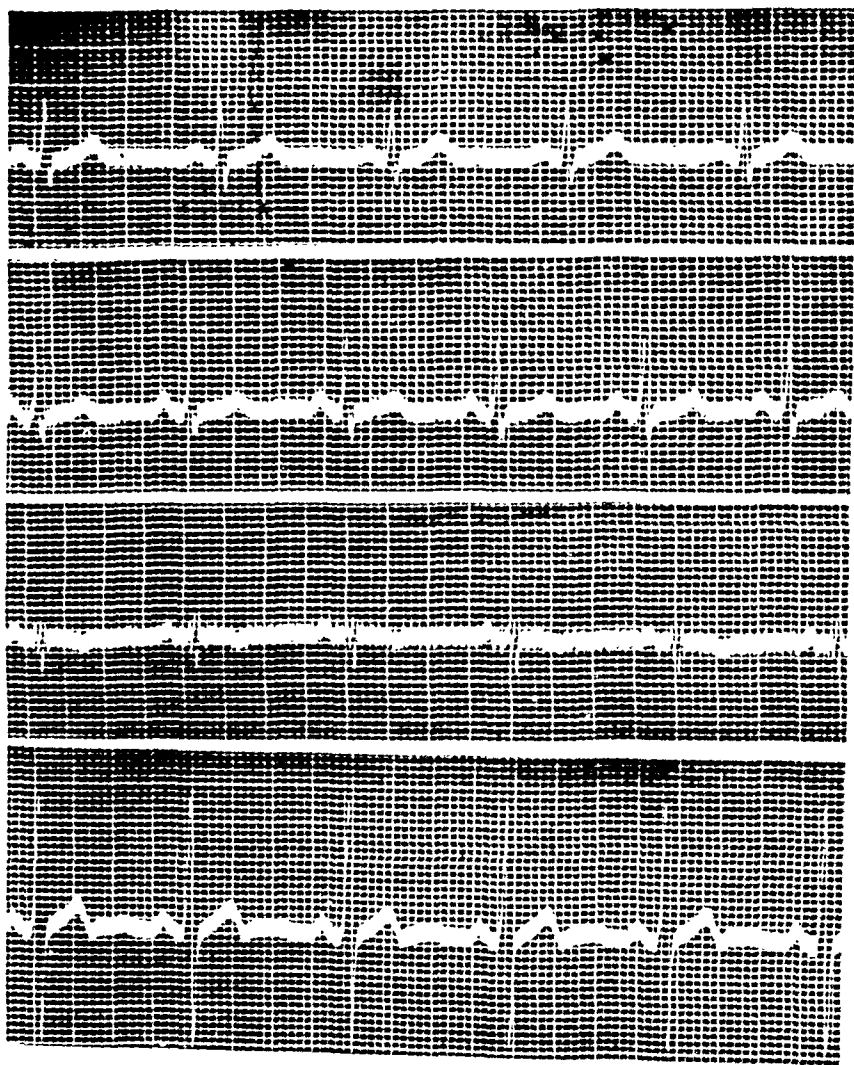


Fig. 7.—February 18, 1939.

CONCLUSIONS

A case of stab wound of the left auricle, with recovery, is reported.

The serial electrocardiograms suggest that electrocardiographic changes incident to injury of the auricles are not essentially different from those caused by injury of other portions of the myocardium, such as occurs after coronary occlusion. The P-wave changes were slight, and not like those ascribed to damage of the mitral valve.

AURICULAR FIBRILLATION OF LONG STANDING, WITH SPONTANEOUS RETURN TO NORMAL SINUS RHYTHM

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IN REVIEWING the literature, only one case was found in which long-standing auricular fibrillation was replaced spontaneously by normal sinus rhythm. This case was reported by Burch,¹ in 1939; the auricular fibrillation had continued for twenty-two months and was succeeded by normal rhythm for a period of nine months. This was followed by a 9-month period of fibrillation, after which normal sinus mechanism was resumed and had continued for a period of four months, at which time the case was reported. Bishop² reported four cases of paroxysmal fibrillation; it is well established that, in such cases, normal sinus rhythm returns within a period of several hours to a week. Brill,³ in a statistical review, stated that 90 per cent of paroxysms of fibrillation may continue for as long as one year and then cease spontaneously. It is commonly agreed that, once established, auricular fibrillation tends to persist throughout life. This case is the second of its kind to be reported. Normal sinus mechanism was resumed after a prolonged period of auricular fibrillation. The change took place spontaneously, without the aid of specific therapy.

CASE REPORT

W. C. B., a physician, aged 74 years, was admitted to the Veterans' Hospital Sept. 30, 1940, for the fourth time. His family history was noncontributory. The wife of the patient stated that she first knew that he had a cardiac ailment about fifteen years before; the exact nature of it she did not know. His personal physician, who examined him regularly prior to his first admission and between subsequent admissions, stated that he was certain that the patient had had a grossly irregular heartbeat for eleven years. His impression was that the irregularity had been present long before that, but he could not be sure because he had no exact records, and no electrocardiograms had been taken. The patient had been taking digitalis at irregular intervals.

He was first admitted on June 15, 1936, with a history of sudden, severe pain about the left kidney which was only partially relieved by barbiturates. The pain radiated to the end of the penis and to the inner aspects of both thighs. This was followed, in twenty-four hours, by bloodtinged urine and then by frank hematuria. He was admitted because of persistence of the pain. Physical examination revealed a well-nourished, 70-year-old white man who was afebrile. The pupils were

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equal, circular, and regular in outline, and reacted readily to light and in accommodation. The ears, nose, and throat were essentially negative. Tenderness was elicited over the frontal sinuses, but further investigation failed to disclose any evidence of sinusitis. The chest was long, broad, and deep, and mobility was good

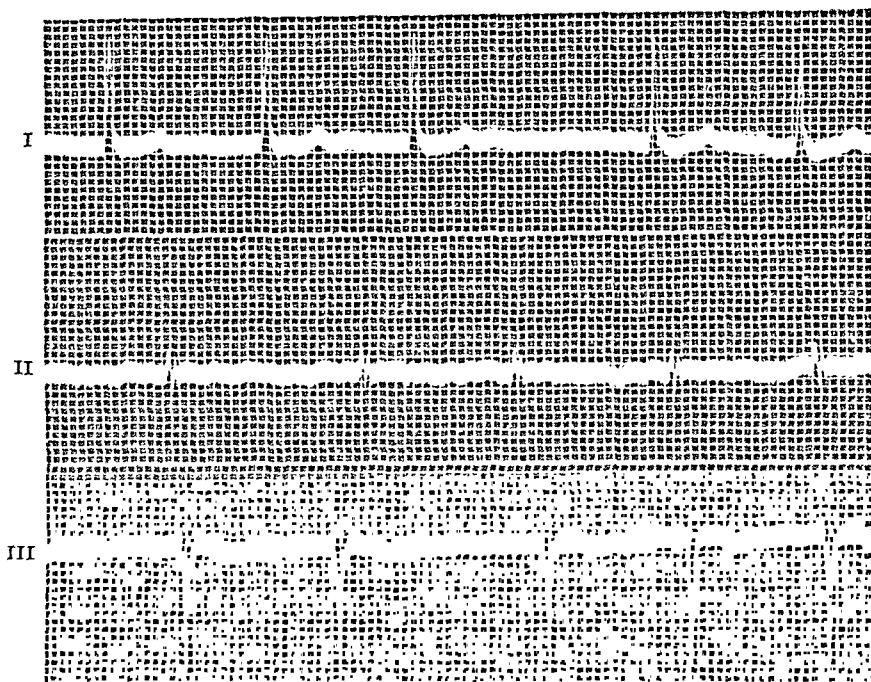


Fig. 1.—June 25, 1936.

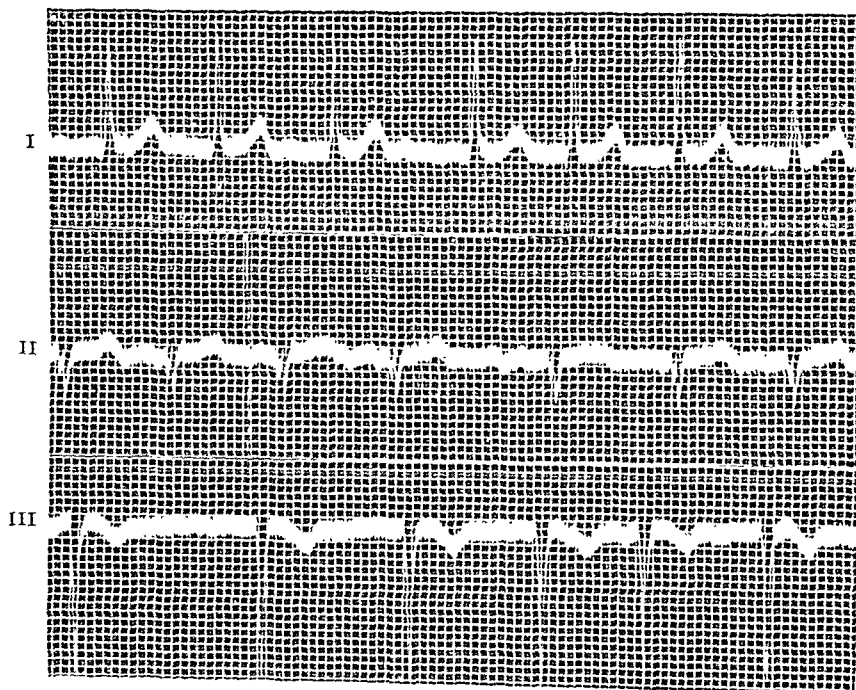


Fig. 2.—Dec. 15, 1938.

and equal on both sides. Expiration was somewhat prolonged and wheezy. No gross abnormalities of the lungs were found. Physical and roentgenologic examination disclosed no evidence of cardiac enlargement. The rate was rapid (108), and the beating was grossly irregular. The blood pressure was 148/102. No murmurs were heard. The abdomen was soft, and no masses were palpable. The liver was neither enlarged nor tender. Deep tenderness was elicited at the left costo-vertebral angle. Small external hemorrhoids were noted. No ankle or pretibial edema was present. The dorsalis pedis pulses were palpable. A blood cell count was not done. Urinalysis disclosed the presence of 3 or 4 erythrocytes per high-power field; these disappeared from the urine in two weeks. The serologic reactions were negative. An electrocardiogram (Fig. 1) disclosed evidence of myocardial damage, left axis deviation, and auricular fibrillation. He was kept on a maintenance dose of digitalis ($1\frac{1}{2}$ grains daily), and was discharged improved on June 29, 1936, with a diagnosis of renal infarction (embolic) secondary to arteriosclerotic heart disease and auricular fibrillation.

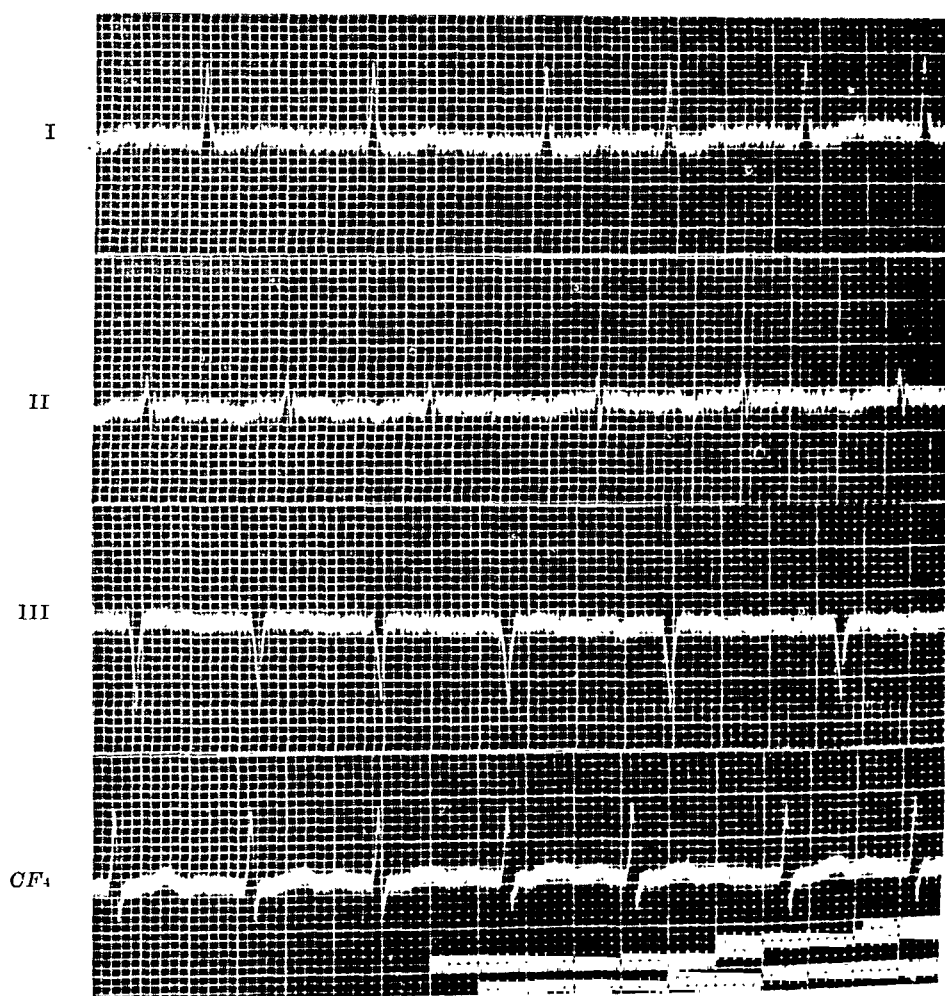


Fig. 3.—Nov. 8, 1940.

He was next seen on Dec. 10, 1938, when he was admitted with symptoms of an acute exacerbation of chronic cholecystitis. Cholecystograms disclosed a nonfunctioning gall bladder. In view of the age of the patient and his general condition, surgical treatment was not advised at that time, and he was treated symptomatically. The cardiac abnormalities were the same as they had been when the

patient was seen in 1936. Auricular fibrillation (Fig. 2) was still present, and the patient was still taking $1\frac{1}{2}$ grains of digitalis daily. He was discharged improved on May 7, 1939.

On June 29, 1939, he was readmitted to have dentures fitted, but no record was made of his cardiac status because of his short stay in the hospital.

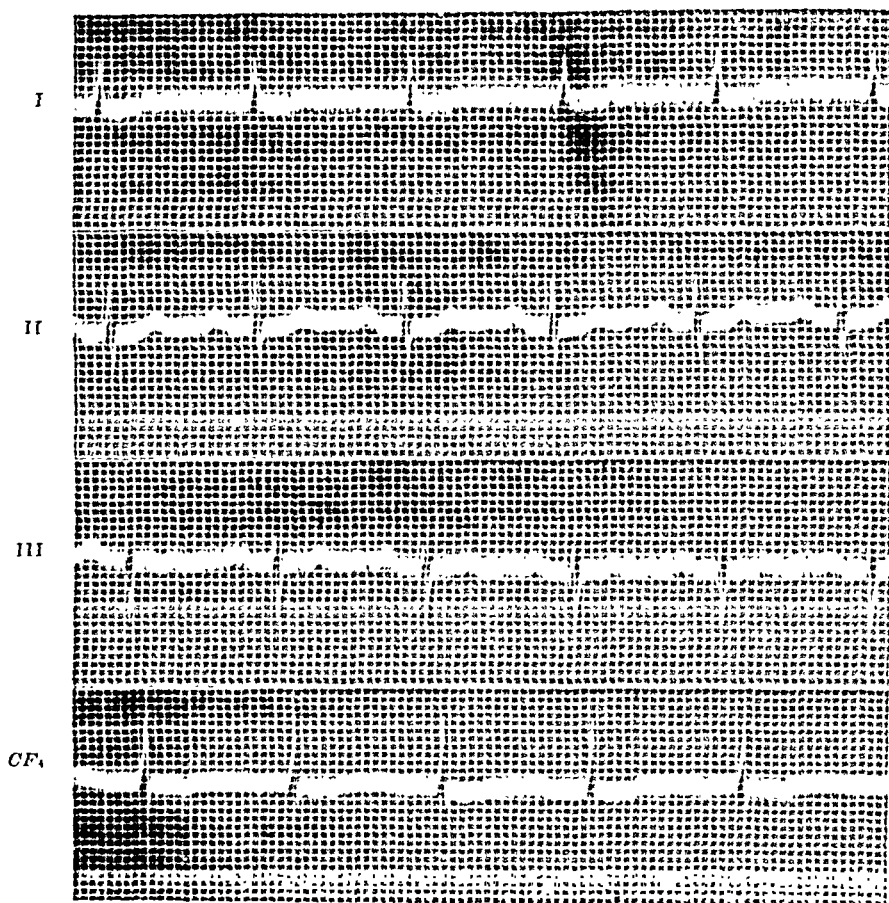


Fig. 4.—Sept. 10, 1911.

The last admission was on Sept. 30, 1940. The history, as given by his wife, was that he had suddenly slumped to the ground while talking to some friends, and that, after the fall, it had been noted that he had right-sided paralysis, with some speech impairment. On admission he was stuporous and acutely ill. Right-sided, flaccid paralysis was present. There were no gross abnormalities of the skull. The pupils were equal, circular, and regular in outline, and reacted readily to light and in accommodation. The ears, nose, and throat were essentially negative. Examination of the chest disclosed dullness at the bases of both lungs, with diminution of the breath sounds and slightly prolonged expiration. No râles were heard. Evidence of atelectasis was found roentgenologically; this disappeared subsequently. The blood pressure was 170/120, and the pulse rate was 106; the pulse was irregular, but there was no pulse deficit. The heart sounds were muffled and no murmurs were heard. There was no evidence of congestive failure. The remainder of the examination showed nothing remarkable. The diagnosis was infarction (embolic) of the left internal capsule, secondary to hypertensive and arteriosclerotic heart disease, with auricular fibrillation. The erythrocyte, leuco-

cyte, and differential leucocyte counts were normal. The serologic reactions were negative. Chemical examination of the urine and blood showed nothing abnormal. He remained in a semicomatose state for two days, but roused enough on the third to take nourishment and try to talk. Digitalis was then continued, depending upon the heart rate. The electrocardiogram (Fig. 3) still showed left axis deviation, evidence of myocardial damage, and auricular fibrillation. The patient improved so much that he could get about with assistance. On Sept. 10, 1941, it was noted that his pulse was regular, and synchronous with the apical beat. An electrocardiogram (Fig. 4) showed normal sinus rhythm. The rhythm has remained normal to date (Fig. 5). Subsequent electrocardiograms, not reproduced here, continued to show normal sinus rhythm.

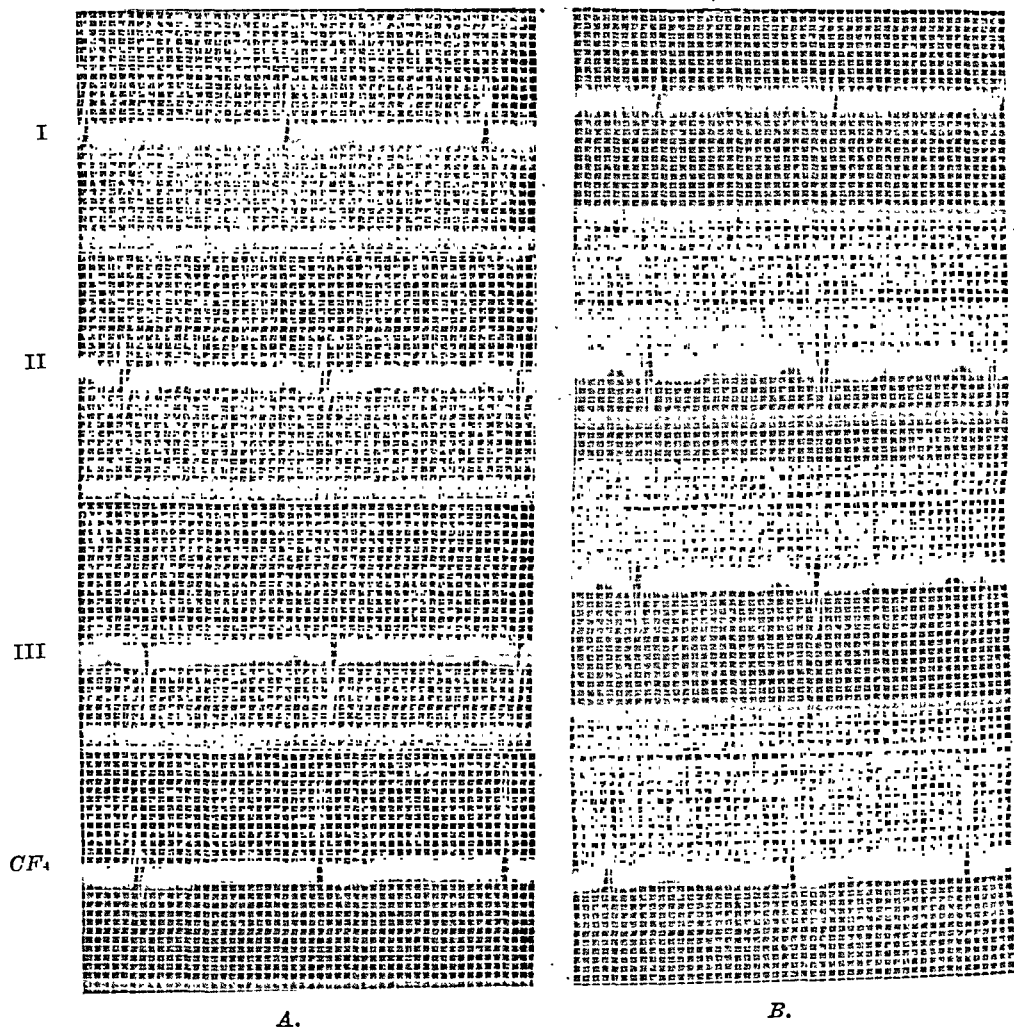


Fig. 5.—A, Oct. 3, 1941. B, Nov. 1, 1941.

DISCUSSION

Auricular fibrillation, from the time of its inception, may be either of two types, i.e., paroxysmal, which may last from several minutes to several days, and persistent or permanent, which tends to continue throughout life. The actual records in this case go back only five and one-half years, but the statement of the patient's personal physician suggests that he had had auricular fibrillation for eleven years. The

statement of the wife that the patient had a cardiac ailment fifteen years earlier is not conclusive, for there is no evidence as to the type and severity of the lesion that existed at that time. During three out of the four periods of hospitalization, clinically and electrocardiographically, auricular fibrillation was demonstrated. The return to normal sinus rhythm was corroborated by the electrocardiogram.

When it was discovered clinically that the heart was beating regularly, it was at first thought that the patient had complete auriculo-ventricular dissociation, in addition to auricular fibrillation. This occurs in some cases of auricular fibrillation during digitalis therapy. This was disproved by the electrocardiogram, which demonstrated the presence of P waves and their absolute regularity with reference to their corresponding QRS complexes. He did not receive digitalis in unusual doses, nor did he receive any quinidine. No unusual drug therapy was instituted at any time. The return to normal sinus rhythm was spontaneous.

CONCLUSIONS

A case in which long-standing auricular fibrillation was replaced by normal sinus rhythm is reported; only one other such case has been reported.

Electrocardiograms taken over a period of five and one-half years are shown, including tracings showing normal sinus rhythm.

The statement of the patient's personal physician indicated that the duration of fibrillation was eleven years.

The return to normal sinus mechanism was spontaneous.

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Abstracts and Reviews

Selected Abstracts

Murphy, Q.: The Influence of the Accelerator Nerves on the Basal Heart Rate of the Dog. *Am. J. Physiol.* 137: 727, 1942.

Many investigators have believed that the cardio-accelerator nerve fibers are in a state of tonic activity. In twenty-four unanesthetized dogs without food for twelve hours and resting for sixty minutes, the basal heart rate or the lowest rate that could be obtained by training was found to range between 42 and 65 beats per minute. Bilateral removal of the stellate and upper five thoracic ganglia failed to result in an appreciable change in the basal heart rate. Under the conditions of these experiments, the accelerator nerves do not seem to be in tonic activity and the accelerator mechanism would seem to be an emergency mechanism.

ROTH.

Katz, L. N., Jochim, K., and Goldman, A.: The Effect of an Injured Area on the Electrical Field of the Heart Based on Experiments With Models. *Am. J. Physiol.* 137: 779, 1942.

The electrical field was explored in models made to represent in simple form the syncytial cell of a normal heart and a heart with an injured, unresponsive area. In the "normal heart" model during electrical diastole the entire external or body field was found to be an equipotential region at the same potential as the external surface of the "polarized cell membrane," i.e., positive with respect to ground. During electrical systole when depolarization was complete the entire field was at ground potential.

In the "injured heart" model during electrical diastole the external field was still positive throughout with respect to ground; however, it was no longer an equipotential region because the "injured region" was only partially polarized. This led to the flow of the resting injury current. During electrical systole the potential distribution in the field was altered due to the depolarization of "uninjured" portions of the "cell membrane," while the "injured region," being unresponsive, retained its partial polarization. This gave rise to the activity injury current. It was shown with these models that distant points in the external field may experience large changes in potential with respect to ground between diastole and systole, and so cannot be considered to be indifferent. Further, the resting injury current and the activity injury current and hence the monophasic curve of injury can be explained in these models on the basis of the classical membrane theory. The activity injury current is shown to be due to the depolarization of uninjured regions and not to any process occurring within the injured area.

AUTHORS.

Hurwitz, M., and Friedberg, L.: Relationship of Heart Size to Cholesterol Content in Experimental Atheromatosis of the Rabbit. *Arch. Path.* 34: 875, 1942.

Anatomically demonstrable sclerosis of the coronary arteries with resultant myocardial fibrosis was produced in rabbits by the feeding of diets high in cholesterol. A comparison of the heart weights of these rabbits with those of a control series

showed, as reported previously, that there is a distinct increase in the size and weight of the heart in the cholesterol-fed group and that this increase is reflected in the percentage of the total body weight comprised by the heart weight.

The hearts of the cholesterol-fed group were analyzed quantitatively for cholesterol and the results compared with those obtained in a control series. It was found that the cholesterol-fed animals showed a definite increase in the cholesterol content of the heart both in the free and in the esterized form. This increase, though unequivocal, could in no way account for the increased weight of the heart.

Since previous studies exclude the dynamic significance of lesions of the aortic valve, and since aortic sclerosis per se does not cause an increase in the work of the left ventricle, it is concluded that myocardial ischemia resulting from atherosclerosis of the coronary arteries per se can be the sole cause of cardiac hypertrophy.

AUTHORS.

Starr, I.: Abnormalities of the Amount of the Circulation (Hyper- and Hypokinemia) and Their Relation to Neurocirculatory Asthenia and Kindred Diagnoses. *Am. J. M. Sc.* 204: 573, 1942.

The author's observations are that the great group of patients with symptoms referable to their circulations, but without disease demonstrated by the usual clinical tests, can be properly divided into three sub-groups depending on the condition of their resting circulations. In the hyper- and hypokinemic groups, and in a few patients of the normokinemic group, the author has demonstrated an abnormality of function which may well be the cause of many of their characteristic symptoms.

Patients with essential hypokinemia have resting circulations similar to those found in many cases of organic heart disease. Therefore it is not surprising that these two groups share many symptoms and that such a term as functional heart disease, which recognizes the similarity, has arisen. Certainly such symptoms as dyspnea on exertion, weakness, dizziness when upright, and susceptibility to fainting attacks, are consistent with the findings of subnormal circulation.

Patients with essential hyperkinemia share their circulatory abnormality with cases of hyperthyroidism, and it is not surprising that they have much the same appearance to gross inspection. Apparently the characteristic appearance of hyperthyroidism, so readily recognized at a glance by experienced clinicians, is more nearly related to the circulation than to the metabolic rate. Perhaps this is why patients with hyperthyroidism complicated by a cardiac disease which has reduced their circulation, may pass so long unrecognized. Without hyperkinemia the characteristic appearance is missing and the attending physician does not immediately see the need of an estimation of basal metabolic rate.

AUTHOR.

Hirsch, S.: Concerning the Finer Structure of the Circular Blood Vessels, Especially the Finding of Autonomic Stretches of Blood Vessels in the Human Heart. *Cardiologia* 6: 105, 1942.

The main stem and the larger branches of the coronary artery are to be considered as an intermediate stage between elastic and muscular artery types. The gradual transition to the muscular type takes place in the medium arteries. The structure of the walls becomes more manifold as the caliber decreases; the special morphological functional circumstances of the supply region are here imprinted histologically. The research carried out under definite technical conditions permits the conclusion that autonomously functioning vessel stretches (glomus) are present in the heart wall, which serve to adjust the current acting on the vessel wall to the changing interstitial pressure of every heart phase (circulation derivative).

AUTHOR.

Evans, W., and Wright, G.: *The Electrocardiogram in Friedreich Disease*. Brit. Heart J. 4: 91, 1942.

The electrocardiogram in 38 patients with Friedreich disease was specially studied. This investigation has convinced us that the condition may sometimes be as much an affection of the heart as of the nervous system.

In only one patient, with Stokes-Adams disease, did clinical examination of the heart show any abnormality; in his case the pulse was slow from complete heart block and irregular from extrasystoles.

Cardioscopy, carried out in all except 4 bedridden patients, showed slight enlargement of the left ventricle in 8, and 5 of these had prominent cardiographic changes.

The cardiogram showed conspicuous or significant changes in 12 of the 38 patients. There were slight changes in another 10. In the remaining 16 the curve was physiological. In the first group 1 patient had complete heart block, 3 had a T_1 type of coronary curve, and 3 had a T_2 type of curve. In 5 the T wave was low and usually inverted in all three limb leads. In 5 of 10 patients showing lesser changes, the S wave was deep and slurred in lead I and usually in lead II, and similarly in leads II and III in the other 5 patients.

When the relation of abnormal signs in the nervous system to the cardiographic changes was examined, it was found that absence of tendon reflexes and extensor response of the plantar reflex were more common in patients with abnormal cardiograms. In respect of other nervous signs it may be said generally that they were more widespread in patients with the more conspicuous cardiographic changes. Of greater significance appeared to be the high incidence of a family history of Friedreich disease in those showing cardiographic changes. Thus 15 out of 22 patients with abnormal cardiograms (8 of them showing gross changes) had one or more relatives, usually a brother or a sister, similarly affected, while only 4 out of 16 patients with normal curves provided this family history. The affected members of the same family tended to show identical cardiographic changes.

The electrocardiogram may help to establish the diagnosis of Friedreich disease when the neurological manifestations are not altogether typical of the condition; an abnormal tracing lends support to the diagnosis, but a normal curve does not exclude it. In prognosis too the cardiogram can be of assistance; when it proves involvement of the bundle of His it may foretell auriculoventricular dissociation and Stokes-Adams disease with its ominous outlook. The exact significance of a "coronary type" of curve is not known yet, but it is probable that only such cases are prone to develop heart failure, although the proximity of this event may be more closely related to the degree of cardiac enlargement, which is best determined by cardioscopy.

For these reasons we would say that the investigation of a patient with Friedreich disease is incomplete without electrocardiography and cardioscopy.

AUTHORS.

Barber, H.: *Electrocardiographic Changes Due to Trauma*. Brit. Heart J. 4: 83, 1942.

A series of 33 hospital accident cases has been examined within two days of the injury. Patients with a severe blow over the chest or a crushing injury of the thorax were selected as opportunity arose.

Eight abnormal electrocardiograms were obtained. The changes observed are comparable with results obtained in animal experiments.

AUTHOR.

Kennedy, J. A.: *A New Concept of the Cause of Patency of the Ductus Arteriosus.* Am. J. M. Sc. 204: 570, 1942.

The cause of closure of the ductus arteriosus at birth is important to the knowledge of physiology and of heart disease.

The author's observations on guinea pigs show that the ductus is different from the other great arteries both histologically and in its physiologic reactions.

The ductus arteriosus during late fetal life is potentially an active structure and is able to close in response to certain definite stimuli.

It normally closes within the few minutes following birth and remains closed. If this normal process of closure is interrupted, patency of ductus arteriosus results. Thus, it may be the interruption of a normal physiologic process which causes this form of congenital heart disease when it occurs alone, not in some bizarre malformation.

AUTHOR.

Hansen, A. E.: *Pleurisy With Effusion as a Manifestation of Rheumatic Fever.* Journal-Lancet 62: 158, 1942.

Pleurisy with effusion characterized a rheumatic recrudescence in a 12-year-old boy who experienced a sudden onset of fever with slight dyspnea and pain in the chest several weeks following a typical attack of polyarthritis. Failure to isolate any organisms in the pleural fluid together with the rapid resorption of the exudate seemed to establish this as a clear-cut rheumatic pleurisy with effusion. This manifestation of rheumatic fever is discussed briefly in relation to other types of pleural effusion, and the protean symptomatology of the serious and all-too-prevalent disease of rheumatic fever is reviewed.

AUTHOR.

Gordon, W. H., Parker, F., Jr., and Weiss, S.: *Gummatous Aortitis.* Arch. Int. Med. 70: 396, 1942.

Three cases of macroscopic gummatous aortitis are reported. In Case 1 the gummatous process of the aorta completely occluded the right coronary artery and partially occluded the left one. In Case 2 gummatous lesions were present also at the base of the aortic valve. In Case 3 an extensive gummatous process affected not only the aorta but the pulmonary artery; the necrotic gummatous lesions resulted in perforation of the aorta into the trachea. In none of these three cases was there gumma in the myocardium.

Gummatous aortitis is mainly localized in the media, but usually the adventitia and the intima are also affected. Macroscopic gummatous aortitis is rare, and the number of authentic cases described in the recent literature, including the three described by us, totals less than ten. In addition to the case reported here of occlusion of the coronary arteries by gumma, only two cases of this condition were found in the literature.

Gummatous lesions of the aorta are responsible for symptoms only if they lead to narrowing or occlusion of the coronary arteries or to perforation of the aorta. Dyspnea, orthopnea, precordial distress, cardiac asthma, pulmonary edema and hemoptysis, when present, are referable to such lesions of the coronary arteries or the aorta.

Of three hundred and sixty cases of chronic syphilitic aortitis, microscopic gummas occurred in eight (1:45). This ratio must be considered minimal. Whether in all cases of chronic aortitis the lesions go through a stage of microscopic gummatous aortitis is not known.

In three of the three hundred and sixty cases of chronic syphilitic aortitis an acute abscesslike lesion was encountered. In a control group of two hundred and twenty-four cases similar "acute aortitis" occurred in six cases (in one associated with mediastinitis, in one with lymphatic leucemia and in four with medionecrosis idiopathica cystica). Chronic lesions of the aorta predispose to secondary acute abscesslike lesions.

The differential morphologic characteristics of gummatous aortitis, on the one hand, and those of acute bacterial aortitis, rheumatic aortitis, tuberculosis of the aorta, atherosclerotic necrosis, medionecrosis idiopathica cystica and aortitis of undetermined origin, on the other hand, are described.

In the group of three hundred and sixty cases of chronic syphilitic aortitis, atheromatous changes over the area affected by the syphilitic lesions were prominent. This suggests that chronic syphilitic lesions of the aorta predispose to the development of local atherosclerosis.

AUTHORS.

Mahaim, I.: Benign Coelothelioma of Tawara's Node. *Cardiologia* 6: 57, 1942.

This is a description of a benign tumor, *sui generis*, of Tawara's node, of which only five observations are known, and which always provokes a heart block. The first time it was described by Mönckeberg under the name of "lymphangioendothelioma," but in fact it is a tumor of embryonic origin which develops from the epicardic coelothelial cells (Deckzellen).

AUTHOR.

Eichna, L. W., and Bordley, James, III. Capillary Blood Pressure in Man. Direct Measurements in the Digits of Normal and Hypertensive Subjects During Vasoconstriction and Vasodilatation Variously Induced. *J. Clin. Investigation* 21: 711, 1942.

The digital capillary blood pressure for all locations in the capillary varied within wide limits, and was qualitatively and quantitatively similar in both normal and hypertensive subjects. This maintained during the following observations which apply equally to both groups of subjects.

Such physiologic influences as neurogenic vasoconstrictions, reactive hyperemia, reflex vasodilatation, and variations in skin temperature between 27° C. and 35° C., all induced such comparatively small changes in the digital capillary blood pressure that the resultant values did not fall beyond "resting" limits. These changes were considerably smaller than the much larger alterations in digital blood flow known to occur under similar circumstances.

Only during increases in local venous pressure did the digital capillary blood pressure consistently exceed "resting" values.

Wide variations in digital capillary blood pressure persisted during reflex vasodilatation, a state during which digital circulation is considered to be full, standard, and reproducible.

During vasodilatation, induced reflexly or by locally injected histamine, there was a disproportionately greater increase in pressure in the venous limb than elsewhere in the capillary. The other states all influenced equally the digital capillary blood pressure in all locations of the capillary.

No correlation existed between the digital capillary blood pressure and the arterial pressure, except perhaps during the hyperemia induced by histamine.

Some mechanism maintains the digital capillary blood pressure within relatively fixed limits, even during marked changes in digital blood flow and arterial pressure.

The similarity of the digital capillary blood pressure of normal and hypertensive subjects indicates that in the digits the increased vascular resistance of hypertensive subjects is precapillary, presumably arteriolar. During the vasodilatation of reactive

hyperemia and reflex vasodilatation, the digital capillary blood pressure was essentially equal in both normal and hypertensive subjects; during vasodilatation induced by locally injected histamine, the capillary pressure to the hypertensive subjects exceeded that in normal subjects. These few experiments may suggest that in the digits histamine appeared to relax, at least to some extent, the increased vascular resistance of hypertension whereas reactive hyperemia and reflex vasodilatation did not.

These data and the conclusions derived therefrom apply only to the capillary blood pressure in the nail-folds of the fingers.

AUTHORS.

Eichna, L. W.: Capillary Blood Pressure in Man. Direct Measurements in the Digits During Arterial Hypertension Induced by Paredrinol Sulfate. J. Clin. Investigation 21: 731, 1942.

During the hypertension induced by paredrinol sulfate in subjects with normal arterial pressures, the digital capillary blood pressure remained within the limits previously established for the same individuals when their arterial pressures were normal.

This finding maintained equally for capillaries in digits with intact innervation and after preganglionic sympathectomy.

At the height of the paredrinol-induced hypertension, the vasodilatation of local reactive hyperemia did not significantly alter the digital capillary blood pressure. The hyperemia of the histamine-flare was usually associated with a rise in the digital capillary blood pressure to values which just exceeded the pressures obtained during the resting state at both normal and elevated arterial pressures.

AUTHOR.

Abell, R. G., and Page, I. H.: The Effects of Renal Hypertension on the Vessels of the Ears of Rabbits. J. Exper. Med. 75: 673, 1942.

Experimental renal hypertension in rabbits causes persistent, visible constriction to occur in the arterioles of the ears which is not great enough to restrict the flow of blood to the tissues but is sufficient to increase peripheral resistance. The constriction is due to the direct action of a substance on the arterioles since it occurs in the absence of nerves to vessels. It is associated with the appearance of new arteriovenous anastomoses. Since many of these phenomena have been reproduced by injection of angiotonin, this evidence is consonant with the view that the hypertension is due to angiotonin or some similar substance.

AUTHORS.

Schroeder, H. A.: "Essential" Hypertension. A Concept of Its Mechanism. Am. J. M. Sc. 204: 734, 1942.

A way of thinking about arterial hypertension has been presented, which takes into account the possible role of renal ischemia and those factors which cause it.

AUTHOR.

Di Palma, Joseph R.: Quantitative Alterations in the Hyperemia Responses to Local Ischemia of the Smallest Blood Vessels of the Human Skin Following Systemic Anoxemia, Hypercapnia, Acidosis, and Alkalosis. J. Exper. Med. 76: 401, 1942.

The responsiveness of the smallest blood vessels of the human skin was measured in systemic anoxemia, hypercapnia, acidosis, and alkalosis. A method was used which measured quantitatively the reactive hyperemia produced by a standardized

period of local ischemia of those fine vessels. By timing the clearing period of the threshold hyperemia response a direct indication of blood flow in these fine vessels was obtained. The following conclusions were reached concerning the responses of the smallest blood vessels of the skin.

Systemic anoxemia causes a decrease in sensitivity to local ischemia and a slowing of the blood flow.

Hypercapnia prevents the changes resulting from anoxemia.

These changes in the smallest blood vessels of the skin occur independently of changes in pulse rate, blood pressure, and respiratory rate and depth.

With systemic acidosis there is a decrease in sensitivity to local ischemia and a slowing of blood flow. The exact opposite takes place in systemic alkalosis.

The view is advanced, after due consideration of the facts, that the carbon dioxide concentration of the blood, or something directly associated with it, is the most important factor determining the sensitivity of these vessels, rather than oxygen saturation or changes in blood pH.

AUTHOR.

Peery, T. M.: Incomplete Rupture of the Aorta: A Heretofore Unrecognized Stage of Dissecting Aneurysm and a Cause of Cardiac Pain and Cardiac Murmurs. *Arch. Int. Med.* 70: 689, 1942.

Incomplete rupture of the aorta is closely akin to dissecting aneurysm; it is the condition which exists after a tear has occurred in the vessel wall but before dissection has begun. It may, in the absence of dissection, cause pain in the chest and sudden dyspnea and is frequently associated with murmurs at the aortic area of the precordium. It is probably more frequent than dissecting aneurysm proper and may or may not be followed by dissecting aneurysm. If incomplete tear was recognized clinically dissection might be prevented in some cases by measures which tend to lower the blood pressure, thus permitting healing of the vessel wall.

The following suggestions may be of help in making an ante-mortem diagnosis of incomplete rupture of the aorta:

If the patient has been under observation for hypertension and returns complaining of sudden suffocation and dyspnea, with or without substernal pain, and if examination discloses either a systolic or a diastolic aortic murmur or both—murmurs which have not been present previously—incomplete aortic rupture should be strongly suspected. A harsh or rasping type of murmur would be particularly suggestive.

If the patient is seen for the first time during an acute attack, the diagnosis of incomplete rupture of the aorta would have to be made largely by exclusion. If no murmurs are detected, an incorrect diagnosis of coronary thrombosis may be made. If there is a diastolic murmur at the aortic area a diagnosis of syphilitic aortic valvulitis may be made, and the pain and suffocation may be assigned to narrowing of the coronary ostiums. The coincidence of hypertension and negative serologic reactions for syphilis may raise some doubt as to the correctness of this diagnosis. The suddenness of onset of symptoms may cause the diagnosis of ruptured aortic valve cusp to be considered. In dissecting aneurysm, which might also be confused with incomplete rupture, pain is usually more severe, and characteristically, the severity and the location of the pain change as dissection continues.

If the patient is seen for the first time because of heart failure due to aortic insufficiency, the correct diagnosis of incomplete aortic rupture would be extremely difficult. If the onset of symptoms of heart failure is sudden, if the patient shows marked hypertension and if clinical evidence of syphilitic and of rheumatic infection is lacking, it may occasionally be possible to make a correct diagnosis of incomplete aortic rupture as the cause of aortic insufficiency.

Careful search of the literature has failed to disclose an instance in which a correct diagnosis of incomplete rupture of the aorta has been made ante mortem.

AUTHOR.

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. VI. Pectin Atheromatosis and Thesaurosis in Rabbits and Dogs. Arch. Path. 34: 883, 1942.

Pectin solutions either freshly prepared and neutralized with phosphate buffer solution or autoclaved and neutralized were injected into dogs and rabbits.

The immediate effects produced on the blood by either of the two solutions are shown in colloidoclastic leucopenia, acceleration of erythrocytic sedimentation and moderate shortening of clotting time.

Repeated injections of pectin solutions do not cause any increase in the viscosity of the plasma or any changes in the number and the ratio of leucocytes.

In dogs and rabbits given injections of the freshly prepared pectin solution, marked foam-cellular storage phenomena develop in the spleen, liver, kidney and marrow in addition to foam-cellular atheromatosis of the various arteries. Older vascular lesions of this origin are characterized by hyaline intimal thickening with or without calcification and by hyaline necrosis and calcification in the media underneath.

Dogs and rabbits given injections of the autoclaved pectin solution showed, on the other hand, with the exception of one rabbit, only minor storage phenomena in the bone marrow and foci of hyaline degeneration and thickening of the arteries.

These differences in degree and type of reaction are due to the fact that pectin solutions are markedly depolymerized when exposed to heat and lose thereby much of their macromolecular characteristics and their original physicochemical properties.

These observations confirm the concept of the presence of a fundamental causal relation between physicochemical colloidal disturbances of the plasma and vascular atheromatosis and organic thesaurosis.

AUTHOR.

Logue, R. B.: Acute Cor Pulmonale. J. M. A. Georgia 31: 163, 1942.

Three case reports of massive pulmonary embolism have been presented, with the electrocardiographic changes which occurred in each. Minimal changes were present in one tracing, the typical McGinn-White type of change was present in another, and in the other serial electrocardiograms simulated those seen in posterior myocardial infarction.

AUTHOR.

Mendlowitz, M.: Clubbing and Hypertrophic Osteoarthropathy. Medicine 21: 269, 1942.

Symmetrical clubbing of the fingers and toes may be acquired in the course of various systemic diseases or may be hereditary. Unilateral and unidigital clubbing apparently occur in association with vascular and vasomotor diseases of the corresponding extremity or finger. Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of the extremities and may develop in any condition capable of producing clubbing.

Characteristic clinical and roentgenological changes occur in clubbing and hypertrophic osteoarthropathy.

Clubbing and hypertrophic osteoarthropathy are seen pathologically to consist chiefly of tissue hypertrophy and hyperplasia. In the original bone, however, osteoclasia and bone resorption may be stimulated.

Hypertrophic osteoarthropathy was produced experimentally in the dog by anastomosis of the pulmonary artery to the left auricle. The most significant circulatory change found was an increase in systemic cardiac output.

Clinical physiological observations have demonstrated in simple acquired symmetrical clubbing an increase in blood flow per unit of tissue caused chiefly by an increased digital arterial pressure. In hereditary clubbing and in hypertrophic osteoarthropathy these changes in digital arterial pressure and blood flow were absent. In unilateral clubbing they were variable.

Previous theories on the pathogenesis of clubbing are reviewed historically and discussed critically.

It is believed that increased peripheral blood flow will form a corner-stone of future theories on the mechanism of clubbing and hypertrophic osteoarthropathy.

AUTHOR.

Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease. Am. J. Roentgenol. 48: 141, 1942.

The diagnosis of dextrocardia with complete or partial transposition of viscera presents no diagnostic difficulties. However, it may be very difficult to differentiate the type of isolated dextrocardia in which there is inversion of the cardiac chambers from that type with a normal arrangement of the chambers. A method of differentiating this type during life is afforded by angiocardiography. The embryology of dextrocardia is discussed and three cases studied by angiocardiography are reported.

WILLIAMS.

Taylor, H. K., and Shulman, I.: Cardio-angiography. Radiology 39: 323, 1942.

Fifteen patients were studied by electrocardiography, the stethogram, venous pressure determinations, circulation tests, kymography, teleroentgenography, and the relatively new method of cardio-angiography. Cardio-angiography visualizes the position of the various components of the heart, and it has been found that their positions are not entirely as described in textbooks. The information obtained from cardio-angiography with respect to the different components of the heart cannot be made available by any one or any combination of the routine methods of cardiac examination. The patients reported included two cases of mild congestive failure, hypertensives, one with renal insufficiency and nitrogenous retention, hypertension with bundle branch block, and a case of coronary occlusion. No serious or untoward reactions occurred. This type of cardiac examination is not recommended in patients who are debilitated, acutely ill, in severe cardiac decompensation, or in those having respiratory distress.

WILLIAMS.

Harrison, J. H.: The Indications and Limitations of Prostatic Surgery in the Presence of Cardiac Disease. Am. J. M. Sc. 204: 469, 1942.

It is now generally agreed that patients having cardiac lesions often tolerate operation unexpectedly well. Indeed, the condition of the circulatory system usually improves immediately on relief of the obstructed bladder. The patient past middle life is not to be considered a poor operative risk for surgery of the prostate merely because of his years. For these reasons a proper evaluation of the factors involved when cardiac disease and urinary obstruction of prostatic origin coexist, is very important.

A careful history is most important in eliciting evidence of heart disease. Studies of exercise tolerance and vital capacity are of value in estimating the operative risk

of elderly patients. The patient who has recently been able to lead an active life is a good operative risk in spite of the presence of heart disease. Acute urinary retention precipitated by an acute cardiac crisis does not always require subsequent prostatectomy. By careful judicious management it is often possible to tide such patients over by conservative means until cardiac decompensation has cleared and normal micturition been resumed.

The patient who tends toward recurrent cardiac decompensation with associated urinary difficulties, has progressively more severe urinary retention with each successive cardiac breakdown. Several weeks should elapse after a coronary accident before resorting to surgery. In general the prognosis is better for these patients who have more than four weeks preoperative preparation, but this period must be judged on the basis of the merits of the individual case.

It is now more often a choice of the proper time to operate and the kind of operation to be employed rather than a decision for or against surgery, because modern methods do not impose a burden on even the diseased heart sufficient to upset its physiologic function when adequate medical care is given. After prostatectomy great improvement is manifested in the cardiovascular condition of the patient who has had urinary retention and heart disease. The operative approach and anesthesia depend on the characteristics and abilities of the patient, surgeon and anesthetist. In this clinic, the transurethral and perineal approaches have been used in recent years almost entirely, except when there is a definite and special indication for the suprapubic operation. The anesthesia of choice has been low spinal or ether.

AUTHOR.

Caviness, V. S., Umphlet, T. L., and Royster, C. L.: Blood Pressure and Sulfo-cyanates (Thiocyanate). *Am. J. M. Sc.* 204: 688, 1942.

Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substance. The concentration is approximately 50,000 times that of nitrites.

Each individual has a fixed constant blood sulfocyanate level.

Blood sulfocyanate concentrations tend to vary inversely with the blood pressure level, whether naturally or under treatment.

There appears to be normally in the body a balance between pressor substances and sulfocyanates. There is a definite tendency for low blood sulfocyanate levels to be associated with hypertension. Higher concentrations of blood sulfocyanates are not associated with hypertension.

Potassium sulfocyanate is a safe depressor substance if used properly; it lowers the diastolic pressure as well as the systolic.

The earlier in the course of the disease that treatment is instituted, the better the results that can be anticipated.

The lower the effective blood sulfocyanate concentration can be kept during treatment, the better the results will be.

The results of this work show such a strong rationale for the use of sulfocyanates in hypertension that the use need no longer be regarded as empirical.

AUTHORS.

Pelner, L.: The Effect of Ascorbic Acid (Vitamin C) on the Sensitivity to Salicylates in a Case of Rheumatic Fever. *J. Lab. & Clin. Med.* 28: 28, 1942.

A severe case of rheumatic carditis became intolerant to sodium salicylate early in the course of the illness.

A low plasma ascorbic acid content, positive tourniquet test, and severe nosebleed suggested the presence of vitamin C deficiency.

The preceding diet of this patient proved to be deficient in vitamin C.

After the vitamin C intake was increased, sodium salicylate was again given in large amounts with impunity.

AUTHOR.

Burstein, J., Brown, G., and Klein, C.: Treatment of Congestive Heart Failure in Ambulatory Patients With an Orally Administered Mercurial Diuretic. *J. Lab. & Clin. Med.* 28: 147, 1942.

Nine patients in congestive heart failure, attending an out-patient cardiac clinic, who were known to be well controlled by administration of intravenous mercurial diuretics, were given instead, an oral preparation of mercurial diuretic in a study to determine the usefulness of this medication in ambulatory patients. Seven of the nine patients (77.7 per cent) showed an increase in urinary output after taking this preparation, as compared with their output when no mercurial diuretic was given. In no case was the increase in urinary output as great as that resulting when the usual dose of a standard mercurial diuretic was given intravenously. Side reactions, chiefly cramps and diarrhea, occurred in six of the nine patients (66.7 per cent) and necessitated discontinuance of administration of the oral mercurial preparation.

AUTHORS.

Lampport, H.: The Effects on Renal Resistance to Blood Flow of Renin, Angiotonin, Pitressin and Atropine, Hypertension, and Toxemia of Pregnancy. *J. Clin. Investigation* 21: 685, 1942.

Pitressin caused no consistent change in glomerular intra-capillary pressure, total effective renal arteriolar resistance, or in the afferent-to-efferent arteriolar resistance ratio in unanesthetized dogs.

Atropine added to pitressin increased total effective arteriolar renal resistance, with afferent arteriolar constriction predominating, in unanesthetized dogs.

Renin infused into unanesthetized dogs increased glomerular intracapillary pressure and total arteriolar resistance with neither afferent nor efferent constriction predominating consistently.

Angiotonin acted rather similarly to renin, but conclusions concerning it are subject to some doubt.

In one test on a human subject, angiotonin caused constriction of both sets of arterioles with afferent constriction predominating.

Afferent arteriolar constriction outweighed efferent constriction more than is normal in all of the seventeen cases of essential hypertension studied.

It is likely that the resistance of the afferent arterioles varies with blood pressure changes so as to preserve renal function.

A specific renal effect is the probable cause of the low filtration fraction seen in late severe toxemia of pregnancy. There is inadequate evidence to decide how much of this effect is primarily constriction of the efferent arterioles and how much, if any, is change in the permeability of the glomerular membrane to water and/or inulin and other sugars.

AUTHOR.

Rosenbaum, J. D.: The Influence of Alterations in Acid-Base Balance Upon Transfers of Carbon Dioxide and Bicarbonate in Man. *J. Clin. Investigation* 21: 735, 1942.

The influence of changes in acid-base equilibrium upon the output of carbon dioxide by the lungs was studied in human subjects.

Overventilation produced large increments in respiratory output of CO_2 . A portion of the CO_2 was given up by the tissues.

Ventilation with a CO_2 -enriched air caused a marked diminution in the volume of CO_2 given out by the lungs. Part of the CO_2 retention was intracellular.

Alterations of the CO_2 content of blood, produced by ingestion of ammonium chloride, may be unassociated with any significant change in the output of carbon dioxide by the lungs.

The volume of distribution of bicarbonate ion administered intravenously as sodium bicarbonate was found to approximate the extracellular fluid volume as determined by the thiocyanate method.

AUTHOR.

Orgain, E. S., and Poston, M. A.: Sulfonamide Compounds in Therapy of Bacterial Endocarditis: A Comparison of the In Vitro Inhibitory Effects and the Bacteriostatic Activity. *Arch. Int. Med.* 70: 777, 1942.

The in vitro inhibitory effects of seven sulfonamide compounds on twenty organisms isolated from seventeen patients suffering from bacterial endocarditis have been correlated with the clinical bacteriostatic activity of these drugs in a series of thirty-three clinical (in vivo) experiments.

A certain degree of correlation was found to exist between the in vitro inhibitory effects of these drugs and their clinical bacteriostatic activity.

The importance of preliminary in vitro experiments to determine the most effective drug and its possible clinical level of inhibitory action is emphasized.

AUTHORS.

Schill, E.: Auricular Flutter Appearing in the Course of a Protracted Treatment With Digitalis. *Cardiologia* 6: 165, 1942.

Description is given of a case in which after a 20-day Verodigen-treatment and direct 8-day intensive treatment with digitalis (pulvis) a temporary attack of arrhythmia perpetua occurred.

AUTHOR.

To Our Readers

The exigencies of the war situation have made it necessary to comply with the order of the War Production Board to reduce the weight of paper previously used for the JOURNAL. While this change will not affect the printed page it will affect the quality of the halftone illustrations. We regret that we have no choice in the matter and would ask the forbearance of our readers. As soon as the restrictions are removed, we shall resume our practice of printing the JOURNAL on the previously employed heavier grade of paper.

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*Executive Committee.

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Original Communications

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

III. EFFECTS ON THE CORONARY BLOOD FLOW*

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THE object of this investigation was to ascertain the effect of therapeutic and toxic doses of digitalis on the coronary blood flow in the intact, trained animal.

LITERATURE

Numerous observations have been made on the effect of digitalis on the extracardiac vessels. Fothergill,¹ Klug,² and Donaldson and Stevens³ stated that digitalis constricted the small vessels in the web of the frog's foot; Legroux⁴ and Boehm,⁵ on the contrary, did not observe any change in the vessels after the administration of digitalis. Legroux, Gourvat,⁶ Klug, and Kraft⁷ described constriction of the blood vessels in the ear of the rabbit; Koppe⁸ stated that the vessels were dilated by digitalis bodies. Ackermann⁹ and Gourvat observed constriction of the mesenteric vessels after the administration of digitalis. Bock¹⁰ reported vasoconstriction in the isolated limbs of dogs after the vessels had been perfused with strophanthin. Jonesen and Loewi¹¹ studied the renal vessels plethysmographically, and observed that digitalis may cause vasodilatation; Joseph,¹² on the contrary, described vasoconstriction in the renal vessels. Eppinger and Hess¹³ and Cow¹⁴ observed constriction of isolated rings of peripheral blood vessels after the administration of digitalis; Rabe¹⁵ found no change or slight constriction in isolated strips of arteries.

Likewise, many studies have been made on the cardiac vessels before and after the administration of digitalis or of allied substances. Eppinger and Hess found that digitoxin, digalen, and strophanthin de-

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

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creased the caliber of rings of coronary artery. Rabe observed constriction of rings of coronary artery. Cow described dilatation of rings of coronary artery after the administration of digitalin. Voegtlin and Macht¹⁶ stated that isolated rings of coronary artery were constricted by digitalin (Merck) and digitoxin (Merck), dilated by digalen, slightly constricted by digitalin (Kiliani), and unchanged by strophanthin (Merck) and strophanthin (Boehringer). Bond¹⁷ and Meyer¹⁸ studied the volume outflow from severed and cannulated superficial coronary veins. Meyer observed that digalen, g-strophanthin, digipuratum soluble, and digistrophan increased the flow, whereas Bond concluded that digitalis and strophanthin did not produce any change in the flow. Gunn¹⁹ did not observe any change in coronary blood flow after the administration of strophanthin; he used the isolated heart of the rabbit and the Condon recorder to measure the flow.

Most of the measurements of coronary blood flow have been made by inserting a Morawitz cannula in the coronary sinus. Sakai and Saneyoshi²⁰ concluded that strophanthin in large doses causes vasoconstriction, whereas, in doses approximating those employed clinically, the drug produces little or no change in the blood flow. Bodo²¹ observed an increase in coronary blood flow after the administration of large doses of tincture of digitalis (10 c.c. to a heart-lung preparation within twenty-six minutes), and also after the administration of 0.3 mg. of strophanthin. Fisher, Guggenheimer, and Müller²² observed a decrease in coronary flow after the administration of strophanthin (0.2 mg., for example). Gilbert and Fenn²³ concluded that ouabain, digitoxin, and tincture of digitalis (even 20 to 30 per cent of the minimal lethal dose) decreased the coronary flow by vasoconstriction. Rühl and Wiehler²⁴ likewise observed vasoconstriction after the administration of strophanthin. Ginsberg, Stoland, and Siler²⁵ found that the administration of digitalis in the Starling preparation decreased the coronary flow for ten minutes, and then increased it.

The thermostromuhr method of Rein²⁶ has been used in recent years to study the coronary blood flow. Hochrein²⁷ stated that digitalis (0.4 c.c. of digipurat) increased the coronary blood flow in some animals and decreased it in others. Essex, Herrick, Baldes, and Mann²⁸ gave approximately 30 per cent of the minimal lethal dose of digiglusin to trained, unanesthetized dogs, and did not observe any significant changes in coronary blood flow as measured by the Baldes-Herrick²⁹ modification of the Rein thermostromuhr. The coronary blood flow was measured daily for a period as long as nine days. Essex, Herrick, and Visscher³⁰ injected solutions containing lanatoside A, B, and C (subnauseating doses, varying from 10 to 20 per cent of the minimal lethal dose) into trained, unanesthetized dogs. With the thermostromuhr method, the coronary blood flow was unchanged. Hildebrandt and Osterwald,³¹ using the Rein thermostromuhr, did not observe any change in coronary flow after 0.15 to 0.5 mg. of strophanthin per kilo-

gram had been administered to dogs anesthetized with morphine and pernocton. This dosage was estimated to be within the therapeutic range; toxic doses caused a decrease of the coronary blood flow, then an increase.

In a critical evaluation of the foregoing experimental methods of measuring coronary blood flow after the administration of digitalis, the following factors deserve comment. The isolated ring method is obviously very unphysiologic. The volume of flow from a severed superficial coronary vein is not a reliable index to the flow of blood in the coronary arteries; too many factors may change the venous flow, with or without a corresponding change of flow in the coronary arteries. The coronary blood flow in the heart-lung preparation may be altered by the effects of the preparatory operative procedure, by the anesthetic agent, and by the fact that the heart usually is denervated.

It must be borne in mind that these experimental methods are adapted to measuring coronary blood flow over periods varying from a few minutes to several hours. They do not permit one to follow the volume of flow over long periods after digitalis has been administered. Furthermore, estimation of the dose of digitalis which would correspond to that ordinarily used in an intact animal or in man is difficult in these experimental preparations.

The thermostromuhr measurements of the coronary blood flow are the only ones which produce values that can be assumed to approach physiologic limits. The trained animals are intact. Their coronary blood flow may be measured at any time during a control period of several days, and at any time over a period of days after the digitalis has been given.

METHODS

In the experiments on blood flow, dogs were used because these animals have coronary arteries which are large enough to permit the application of the thermostromuhr unit.

Fourteen dogs were prepared for these experiments, six of which were satisfactory for observations on the coronary blood flow. Seven animals were unsatisfactory for the following reasons: development of postoperative complications (three dogs), occlusion of the vessels under the thermostromuhr unit (one dog), malfunction of the unit (one dog), a break in the lead wires from the unit within the animal's thorax (one dog), and disjunction of the unit and the coronary artery, so that the former lay free in the thoracic cavity (one dog). One animal which did not have a unit applied to the coronary artery was used for measurements of blood pressure before and after the administration of a toxic dose of digitalis.

The sequence of experimental procedures used to obtain the coronary blood flow readings may be summarized briefly:

1. Each animal was trained to lie quietly on its right side on a table. Several days were required to train the average dog.

2. The Rein thermostromuhr unit (as modified by Baldes and Herrick) was applied to the circumflex branch of the left coronary artery while the animal was under general anesthesia and was connected with an artificial respirator. Sterile operative technique was used to expose the heart through an incision between the fifth and sixth ribs on the left side. A short segment of the previously mentioned coronary artery was carefully dissected free from the adjacent tissue. A thermostromuhr unit of the proper size was fastened to this isolated portion of the coronary

artery. In addition, the lead wires from the unit were sutured to the epicardium to aid in stabilizing the unit on the coronary artery. The pericardium and the chest wall were then closed with sutures. The lead wires from the unit were permitted to emerge from the anterior (ventral) portion of the incision.

3. After the animal had recovered sufficiently from the immediate effects of the operation (twenty-four to forty-eight hours), had attained its approximately normal body temperature, had regained its appetite, and had been able to run about the laboratory without any apparent discomfort or illness, daily measurements of the coronary blood flow were made. Before the reading of the blood flow was made each day, the animal was made to lie quietly on a table for thirty minutes to one hour in order to obtain, as nearly as possible, a basal value for the coronary blood flow.

4. When the daily measurements of the coronary blood flow remained fairly constant, the appropriate dose of digitalis was injected intravenously. The intravenous route was chosen in order to make certain that all of the drug, in any given dose, entered the circulation.

5. After the digitalis had been administered, daily measurements of the coronary blood flow were made. (Each animal was made to lie quietly on the table until a sustained basal flow reading was obtained.) In some of the animals, measurements of blood flow were made at intervals of one hour during the first six to eight hours after the drug had been injected. Nausea and vomiting, however, limited the value of these immediate readings.

6. The experiment was terminated when the lead wires broke within the thoracic cavity, or when the animal was killed in order to study the myocardium grossly and microscopically.

In selecting the animals, an endeavor was made to use old dogs. It had already been shown³² that old cats are more sensitive to digitalis than young ones.

The animals were fed daily after the blood flow had been measured.

The construction of the thermostromuhr unit and its calibration have been described by Rein, Baldes and Herrick, and Herrick and Baldes,³³ and the description need not be repeated here.

Measurements of blood pressure were made on some of the animals with the manometer technique of Hamilton, Brewer, and Brotman.³⁴

The digitalis preparations which we used were as follows: (1) digifoline, 2 c.c. = 1 cat unit; (2) digalen, 2 c.c. = 1 cat unit; (3) digitoxin, 0.575 mg. per kilogram of dog = minimal lethal dose; (4) lanatoside A, 0.437 mg. per kilogram of dog = minimal lethal dose.

It was estimated that 30 per cent of the minimal lethal dose was equivalent to the "calculated therapeutic dose." Eighty per cent of the minimal lethal dose was definitely toxic. It has been shown³² that 80 per cent of the minimal lethal dose of digitalis may produce histologic changes in the heart of the cat. The lethal dose of digitalis for the dog was taken to be approximately 25 per cent greater than that for the cat.

RESULTS

Care was taken to use only those animals which had recovered from the operative procedure and were, to all intents and purposes, in good condition. An endeavor was made to keep the animal as quiet as possible when the measurements of average minimal blood flow were made each day.

A. Effects of Calculated Therapeutic Doses of Digitalis on the Coronary Blood Flow.—In confirmation of the work of Essex, Herrick, Baldes, and Mann,²⁸ the estimated therapeutic dose of digitalis (30 per

cent of the minimal lethal dose of digalen) did not produce any significant change in blood flow in the circumflex branch of the left coronary artery over a period of three days (Fig. 1 and Table I). There was no significant change in coronary blood flow after the administration of 30 per cent of the minimal lethal dose of digitoxin over a period of three days (Fig. 2).

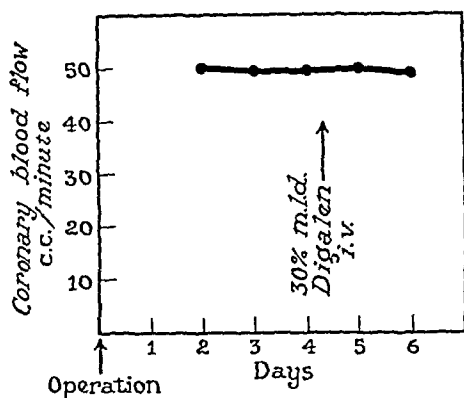


Fig. 1.—No change in coronary blood flow after intravenous administration of calculated therapeutic dose of digitalis (30 per cent of minimal lethal dose of digalen). No histologic changes were found in the myocardium of this animal.

TABLE I

CORONARY BLOOD FLOW OF A 15-KILOGRAM DOG AFTER THE INJECTION OF A CALCULATED THERAPEUTIC DOSE OF DIGITALIS (30 PER CENT OF MINIMAL LETHAL DOSE OF DIGALEN)

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	AVERAGE BLOOD FLOW, C.C. PER MINUTE	TIME OBSERVED AFTER OPERATION	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPERATURE, DEGREES F.	REMARKS
	50.2	48 hr. (2 days)	130	103.2	
	49.7	72 hr. (3 days)	132	103.0	
	49.4	96 hr. (4 days)	108		Animal's condition satisfactory
30% digalen		103 hr.			
	50	120 hr. (5 days)			Note no change of rate of flow with calculated therapeutic dose
	49	144 hr. (6 days)	100	102	Mechanical break in lead wires
		168 hr.			

B. Effects of Toxic Doses of Digitalis on the Coronary Blood Flow.—Fig. 2 and Table II indicate that, although a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose of digitoxin) did not change the coronary blood flow, a toxic amount of the drug (63 per cent of the minimal lethal dose of digitoxin) decreased the volume of flow from 96 to 61 c.c. per minute. The decrease of blood

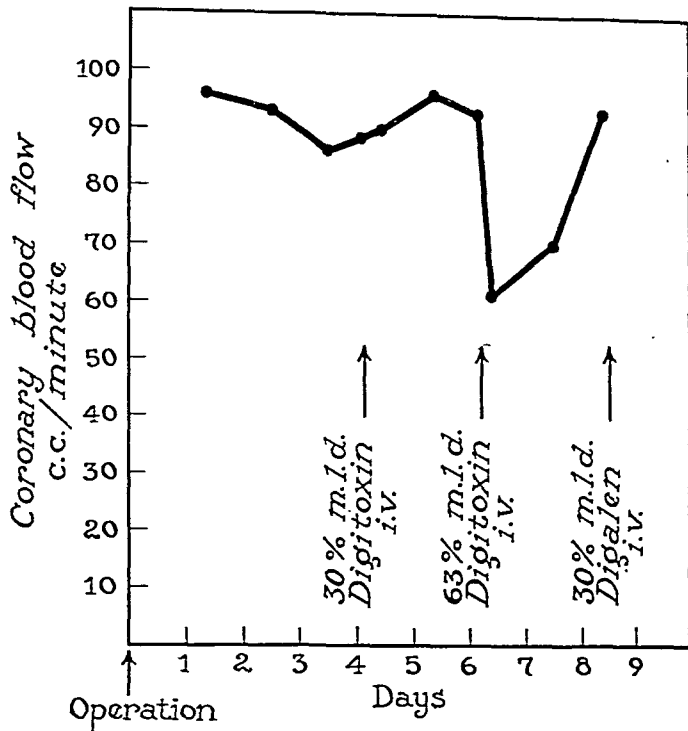


Fig. 2.—No significant change in coronary blood flow after intravenous administration of calculated therapeutic dose of digitalis (30 per cent of minimal lethal dose of digitoxin). Decrease of coronary blood flow after intravenous administration of toxic dose of digitalis (63 per cent of minimal lethal dose of digitoxin); the diminution of coronary blood flow was not sustained. The animal died promptly after injection of third dose of drug. No myocardial lesions were found.

TABLE II

CORONARY BLOOD FLOW OF A 26-KILOGRAM DOG AFTER THE INJECTION OF A THERAPEUTIC DOSE OF DIGITALIS (30 PER CENT OF MINIMAL LETHAL DOSE OF DIGITOXIN) AND AFTER INJECTION OF TOXIC DOSE OF DIGITALIS (63 PER CENT OF MINIMAL LETHAL DOSE OF DIGITOXIN)

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPER- ATURE, DEGREES F.	TIME OBSERVED AFTER OPERATION	REMARKS
	96	126	102.8	32 hr. (1 day+)	
	93	126	101.6	59 hr. (2 days+)	Excellent condition. Aver- age control flow 90.6 c.c.
	86	100	101.6	82 hr. (3 days+)	
	88	106	101.6	97 hr. (4 days+)	
30% digitoxin					
	90	72	101.4	106 hr.	8 hr. after digitoxin; no decrease flow
	96	126	101.8	128 hr. (5 days+)	
63% digitoxin					
	61	68	101.4	152 hr. (6 days+)	Numerous premature con- tractions
	70	66		179 hr. (7th day)	Numerous premature contractions
	93	156	102	203 hr. (8th day)	Regular, but rapid, pulse. Dog was given 30% of minimal lethal dose of digalen intrave- nously. Died promptly

flow was not sustained; forty-eight hours after the toxic dose had been injected, the blood flow had returned to its previous level, i.e., 93 c.c. per minute. A third injection of 30 per cent of the minimal lethal dose of digalen caused the animal to die within a few hours. No histologic changes were observed in the heart of this animal.

Table III shows a marked increase in coronary blood flow during the stage of nausea. The blood flow increased from 160 to 285 c.c. per

TABLE III

CORONARY BLOOD FLOW OF AN 18.4 KILOGRAM DOG AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS (80 PER CENT OF MINIMAL LETHAL DOSE OF DIGALEN)

Note rise of coronary blood flow in stage of nausea and fall of blood flow in postnausea stage

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	TIME OBSERVED AFTER OPERATION	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	BLOOD PRES- SURE, MM. HG	RECTAL TEMPER- ATURE, DEGREES F.	REMARKS
	48 hr. (2nd day)	168	86		101.8	
	82 hr. (3rd day)	155	90	198/112	101.8	Average control flow, 162.7 c.c. per minute
	88 hr. (3rd day)	165	86			
	96 hr. (4th day)	163.5	78		101.8	
	101 hr. (4th day)	160	78		101.6	
80% digalen	4th day	160	64			Restless; uncomfort- able
	½ hr. after injection					Restless; nausea- ated, emesis
	1 hr. after injection	285				Nausea and vomit- ing
	2 hr. after injection	235	138			No emesis past hr. Restless
	3 hr. after injection	172	124			Extrasystoles. Eme- sis within hr. Quiet
	4 hr. after injection	140	100			Quiet
	8 hr. after injection	105	120			Maximal decrease of flow recorded
	132 hr. (5th day)	144	94		101.4	Extrasystoles. Dog restless. Not basal value
	156 hr. (6th day)	128	96	202/117	101.2	Quiet
	179 hr. (7th day)	134	78		101.3	Extrasystoles. Quiet
	190 hr. (8th day)	132	74		101.2	Dog quiet. Lead wires to unit broken inside chest. Dog re- covered

minute one hour after the administration of a toxic dose of digitalis (80 per cent of minimal lethal dose of digalen). Eight hours after the

TABLE IV

DECREASE IN CORONARY BLOOD FLOW IN A 13.3-KILOGRAM DOG

Decrease was maintained over a period of days by repeated doses of digitalis in the toxic range

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	TIME OBSERVED AFTER OPERATION	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPER- ATURE, DEGREES F.	REMARKS
	23 hr.	51.2			
	31 hr.	52.5	130	104	Condition fair (average control flow, 52.3 c.c. per minute)
	48 hr. (2 days)	51.6	120	103.2	
	72 hr. (3 days)	54	120	102.4	
80% digitoxin	73 hr.		32		Pulse rate 32, 20 minutes after injection
	78 hr.	38	102	102.4	6 hr. after injection of digitoxin
	96 hr. (4 days)	36	66	102.4	24 hr. after injection of digitoxin. Bigeminal pulse
	120 hr. (5 days)	34.6	82		48 hr. after injection of digitoxin. Extrasystoles
	144 hr. (6 days)	32.6	70	102.4	74 hr. after injection of digitoxin. Regular pulse
	168 hr. (7 days)	38	78	103.1	96 hr. after injection of digitoxin. Animal seems in good condition
	192 hr. (8 days)	38	80	102.6	120 hr. after injection of digitoxin
	216 hr. (9 days)	36	66		
30% digitoxin	217 hr.				
	224 hr. (9 days)	32.6	66	102.2	24 hr. after 2nd injection digitoxin
	240 hr. (10 days)	33		103.2	48 hr. after 2nd injection digitoxin
	264 hr. (11 days)	29.5	64	102.4	72 hr. after 2nd injection digitoxin
40% digitoxin	265 hr.				
	288 hr. (12 days)	36.8	128		Note rapid rate heart
	312 hr. (13 days)	27	64	101.8	Maximal decrease of flow 48%
	336 hr. (14 days)	27.2	64	102.2	Extrasystoles. Dog seems in good condition
	384 hr.	30.5	72	102.2	Dog killed to study myocardium microscopically

drug had been injected the coronary blood flow was decreased to 105 c.c. per minute. During the next four days the flow rose gradually to 132 c.c. per minute. The experiment was terminated when the wires to the thermostromuhr unit were broken within the thoracic cavity of the animal. The unit was removed from the coronary artery and the animal recovered completely.

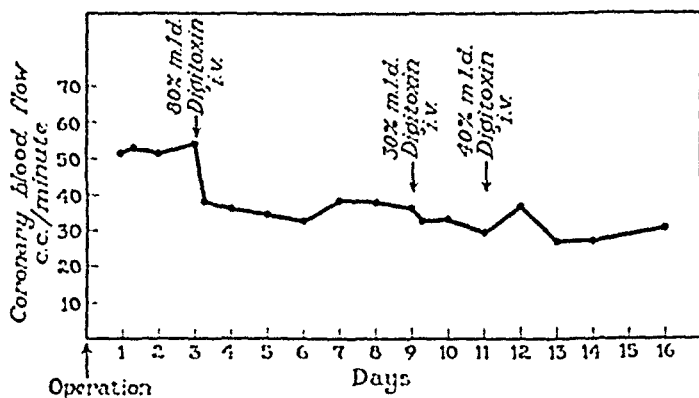


Fig. 3.—Decrease in coronary blood flow after administration of toxic doses of digitalis. The doses of digitalis bodies were spaced in an endeavor to maintain the coronary blood flow below the control level. Histologic changes were found in the myocardium.

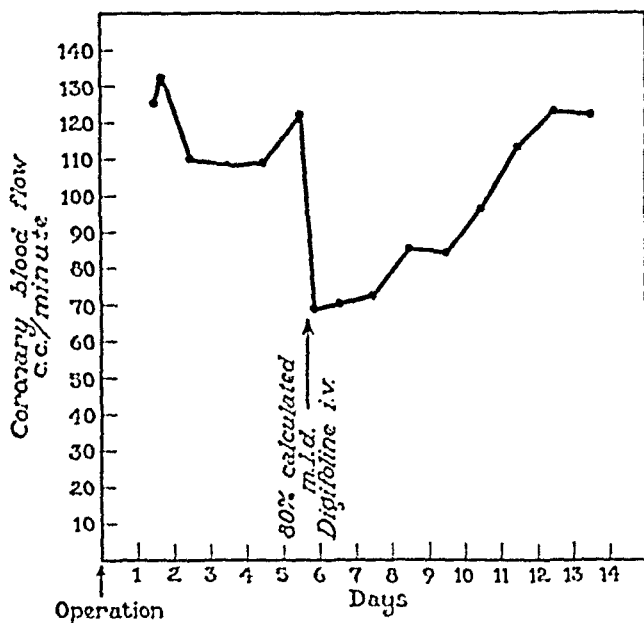


Fig. 4.—Decrease in coronary blood flow after administration of a single toxic dose of digitalis. Note that the coronary blood flow returned to the preinjection levels. The animal recovered completely.

Fig. 3 and Table IV also show a decrease in coronary blood flow after the administration of toxic doses of digitalis (digitoxin). In this experiment, an endeavor was made to maintain the coronary blood flow below the control level for a prolonged period (fourteen days). Fig. 3 is self-explanatory. The animal was killed in an ether chamber on

the sixteenth day of the experiment so that the myocardium might be studied microscopically. Histologic changes were observed in the left ventricular wall and in the interventricular septum. These anatomic changes were similar to those described in the first paper of this series.³² There was no evidence of occlusion of the coronary artery, either directly within the unit or elsewhere along the course of the vessel.

In order to make more certain that the decrease of coronary blood flow was not caused by intravascular thrombosis within the thermo-

TABLE V

DECREASE IN CORONARY BLOOD FLOW AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS; RETURN OF FLOW TO THE APPROXIMATE CONTROL LEVEL AFTER A PERIOD OF DAYS

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	TIME OBSERVED AFTER OPERATION	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPER- ATURE, DEGREES F.	REMARKS
	24 hr. (1 day)	175	106	102.2	Restless. Not basal
	48 hr. (2 days)	100	98	102.2	
	72 hr. (3 days)	120	80	102.2	Average = 113 c.c. per minute
	96 hr. (4 days)	120	84	102.4	
	120 hr. (5 days)	112	48	102.0	
	128 hr.	113	54		
80% lanatoside A	144 hr. (6 days)	88.5	88	100.0	Vomited in morning 14 hr. after injection of lanatoside A
	168 hr. (7 days)	101	72	101.6	Restless—not basal flow.
	192 hr. (8 days)	68	46	101.0	Pulse regular
	216 hr. (9 days)	72	46	101.6	Bigeminal pulse
	240 hr. (10 days)	72	58	101.2	Bigeminal pulse
	264 hr. (11 days)	90	49	101.6	Regular pulse. Restless
	288 hr. (12 days)	82			Animal in good condition
	312 hr. (13 days)	96	50	101.1	
	360 hr. (15 days)	100	66		Pulse irregular (extra- systoles)
	384 hr. (16 days)	100.1	66		Pulse irregular (extra- systoles)
	17 days				Wires broken to heater and thermocouple. Unit removed from vessel 20 days after operation. Vessel patent. Animal recovered; wound healed in few days

stromuhr unit, two old animals were given single toxic doses of digitalis, after which the measurements of blood flow were made daily until the values reached the preinjection readings. Fig. 4 and Tables V and VI give the results of these two experiments. Both animals recovered completely. No evidence of intravascular thrombosis was noted within the units when the latter were removed from the coronary vessels.

Our data do not permit a definite explanation for the behavior of the coronary blood flow in these two experiments.

C. Observations on Blood Pressure, Pulse Rate, and Coronary Blood Flow After the Administration of Toxic Doses of Digitalis.—No definite

TABLE VI

DECREASE IN CORONARY BLOOD FLOW OF A 15-KILOGRAM DOG AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS; RETURN OF CORONARY BLOOD FLOW TO THE PREINJECTION LEVEL AFTER A PERIOD OF DAYS

Blood pressure and pulse rate are recorded

OP. 9/25/40 10:30 A.M.	DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	AVERAGE BLOOD FLOW, C.C. PER MINUTE	BLOOD PRES- SURE, MM. HG	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPER- ATURE, DEGREES F.	REMARKS
9/26/40 10:30 a.m.		128		108	103.0	Animal restless
9/27/40		110		98	103.4	
9/28/40 12:00 m.		108		76	102.2	Animal quiet
9/29/40 2:30 p.m.		108		82	102.4	Restless
9/30/40 12:00 m.	80% digifoline	122	223/110	82	102.2	Restless
9/30/40		69		80	102.2	
10/ 1/40 1:30 p.m.		70	157/100	132	101.8	Quiet
10/ 2/40 2:00 p.m.		72	187/102	62	101.8	
10/ 3/40 2:00 p.m.		85	204/100	76		
10/ 4/40 2:00 p.m.		84	192/99	66	102.0	Animal in excellent health
10/ 5/40 2:00 p.m.		96		72	101.8	
10/ 6/40 2:00 p.m.		113		68	102.0	
10/ 7/40 2:00 p.m.		123		76		
10/ 8/40 2:00 p.m.		122	215/104	70		Animal quiet; re- covered
10/15/40			225/117	123		
10/22/40			205/117	147		
10/30/40	80% digifoline					
10/31/40			138/92	147		
11/ 1/40			206/95	57		
11/ 2/40			191/104	93		
11/ 4/40			226/112	63		

correlation could be established between the blood pressure or pulse rate and the decrease of coronary blood flow after the administration of toxic doses of digitalis to trained dogs.

Table III shows that the blood pressure two days after injection of a toxic dose of digitalis (80 per cent of the minimal lethal dose of digalen) was approximately the same as the control reading although the coronary blood flow had not yet returned to the preinjection value. The pulse rate during the preinjection recording of blood pressure was approximately the same as it was two days after the toxic dose of digitalis had been administered.

In one case there was a lack of significant change in blood pressure two days after a toxic dose of digitalis (80 per cent of minimal lethal dose of digalen) had been administered. The blood pressure before injection was 228/128 (pulse rate = 132 per minute); two days after the injection it was 214/121 (pulse rate = 96 per minute). Measurements of coronary blood flow were not made in this case.

Table II shows that there was a decrease of pulse rate after the injection of a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose of digitoxin), but no further decline of pulse rate occurred when a toxic dose of digitalis (63 per cent of the minimal lethal dose of digitoxin) was administered to the animal. The blood pressure was 171/98 the day before the toxic dose was given, and 178/93 the day after the toxic dose had been administered. Although the blood pressure did not change significantly, the coronary blood flow was decreased from 96 to 61 c.c. per minute on the day these measurements of blood pressure were made. In this experiment the pulse rate fell from 126 to 66 per minute.

Table VI shows a decrease of blood pressure on two occasions after toxic doses of digitalis had been given. On the first occasion the blood pressure was 223/110, and coronary blood flow, 122 c.c. per minute, before the digitalis was administered. The day after the injection of 80 per cent of the minimal lethal dose of digifoline the blood pressure fell to 157/100, and the coronary blood flow was decreased to 70 c.c. per minute. The change in blood pressure was primarily in the systolic level; the change in the diastolic pressure was not very significant. On the second occasion the fall of blood pressure was more striking. A month was permitted to elapse between the first and the second injection of digitalis. The blood pressure was 205/117 (pulse rate = 147 per minute) before the second injection of 80 per cent of the minimal lethal dose of digifoline; the pressure fell to 138/92 (pulse rate = 147 per minute) the day after the administration of the drug.

A series of control readings of blood pressure were made on an animal over a period of seventeen days (Table VII); then a toxic dose of digitalis (80 per cent of the minimal lethal dose of digifoline) was injected intravenously. No significant change in the blood pressure was observed during the next thirty days. The pulse rate values are also recorded in Table VII.

TABLE VII

BLOOD PRESSURE AND PULSE RATE BEFORE AND AFTER THE INJECTION OF A
TOXIC DOSE OF DIGITALIS

DATE OBSERVED	BLOOD PRESSURE, MM. HG	PULSE RATE, BEATS PER MINUTE	BODY TEMPERATURE, DEGREES F.
9/18/40	219/104	104	102.6
9/20/40	215/105	105	101.2
9/23/40	209/116	124	101.8
9/25/40	225/109	105	102.0
9/27/40	213/116	105	101.2
10/ 2/40	222/109	108	101.8
10/ 5/40	221/114	129	102.0
10/ 7/40	80% of minimal lethal dose of digifoline intravenously		
10/ 8/40	229/110	96	101.0
10/10/40	231/117	90	101.8
10/15/40	209/124	150	101.6
10/22/40	184/100	148	101.6
10/31/40	206/96	96	102.0
11/ 7/40	204/100	117	101.2
11/12/40	247/109	114	102.0
11/20/40	204/116	111	101.8
11/27/40	214/103	102	102.0
12/ 4/40	209/103	102	101.0
12/ 9/40	220/103	93	101.2

COMMENT

One of the most likely sources of error in these experiments is in estimating the dose of digitalis for the dog which will correspond to any given dose of the drug in man. It is to be remembered that the dog is less sensitive to digitalis than the cat, and probably also is less sensitive to the drug than man. For the lack of a better method, we have expressed the quantity of digitalis in terms of the minimal lethal dose for the dog. Sources of error in the technical procedure involved in the thermostromuhr method of measuring coronary blood flow were minimized as much as possible. The units were selected and calibrated carefully. They were applied snugly to the coronary artery and anchored securely to avoid compression of the vessel.

Control readings were made after the animals had recovered from the immediate effects of the operation and were observed to be free from significant postoperative complications. The body temperature and the cardiac rate were recorded in all cases. Estimations of blood pressure were made in some cases in order to ascertain whether variations in systemic pressure might be contributing to the changes in coronary blood flow.

The individual measurements of the coronary blood flow were often checked by independent observers and the results compared.

Care was taken to have the animal in as nearly a basal state as possible before each final measurement of the coronary blood flow was made each day. If the animal was restless, the measurements of coronary blood flow were variable and unsatisfactory.

We wish to avoid an error in the interpretation of our experiments

by stating that we are uncertain of the mechanism by which the coronary blood flow is decreased by toxic doses of digitalis or is maintained at a level below the control readings for periods of days.

SUMMARY

Calculated therapeutic doses of digitalis did not produce a significant change in the coronary blood flow of the dog. This confirms the results of Essex, Herrick, Baldes, and Mann.²⁸

Calculated toxic doses of digitalis decreased the coronary blood flow of dogs four to six hours after the drug had been administered. The diminution of flow persisted for several days after a single toxic dose of the drug.

No myocardial lesions were observed after a therapeutic dose of digitalis, nor were they observed in one animal which received a toxic dose of digitalis. In the latter animal the coronary blood flow returned to the preinjection level within two days.

Myocardial lesions were observed in one animal in which the coronary blood flow was kept well below the control level for twelve days by repeated injections of digitalis (toxic range).

The diminution of coronary blood flow after the injection of toxic doses of digitalis could not be correlated consistently with changes in the pulse rate or systemic blood pressure.

After the injection of toxic doses of digitalis the coronary blood flow returned to the control level in several experiments, and the animals recovered completely.

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EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

IV. EFFECTS ON THE CELLULAR STRUCTURE OF THE CENTRAL NERVOUS SYSTEM*

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THE purpose of the following studies was to ascertain whether therapeutic and toxic doses of digitalis are capable of producing demonstrable histologic changes in the brain and spinal cord of experimental animals. It is well known that digitalis in toxic amounts may produce transitory psychoses and other signs of cerebral disturbance among elderly patients. The question is raised whether some of these cerebral symptoms may not have their origin in structural as well as functional changes in the nerve cells of the brain.

LITERATURE

Withering,¹ who was the first physician to describe adequately the clinical use of digitalis, observed that the drug in toxic amounts affected the nervous system. He stated, "The foxglove when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death."

Since this publication, numerous writers have called attention to cerebral symptoms among patients who have received digitalis. Duroziez² reported twenty cases of "coma digitaliques." Hall^{3, 4} described hallucinations and delirium in two patients who had received digitalis. Mackenzie⁵ referred to headaches as the most frequent effect of digitalis on the central nervous system; he described several patients who exhibited "curious cerebral attacks." Hamburger,⁶ in a study of five patients who had "acute cardiac psychoses," concluded that digitalis may contribute to a confusional state in patients whose circulation already is embarrassed severely. Carr⁷ reported two cases of delirium caused by digitalis, and pointed out several important features on which the diagnosis depended. Plummer⁸ warned against the over-

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digitalization of elderly patients. He attributed some of the deaths of patients suffering from cardiac disease to the toxic action of digitalis on the central nervous system. Christian,⁹ Peabody,¹⁰ and Conner¹¹ expressed similar opinions regarding the cerebral toxic effects of digitalis. Weiss¹² observed six instances of toxic psychoses among three hundred patients who received "up to toxic doses of digitalis." He attributed the psychosis to a sudden change of the cerebral circulation and to the physiochemical changes associated with the removal of large amounts of edema from the brain. Willius¹³ called attention to the ominous nature of manifestations in the central nervous system after the administration of toxic doses of digitalis. Luten¹⁴ stated that it was an open question whether the cerebral manifestations of digitalis intoxication were dependent on cerebral vascular effects or on direct action of digitalis on the brain.

We are not aware of any anatomic studies on the central nervous system of man or animals after the administration of toxic doses of digitalis.

METHODS

The same animals on which the anatomic studies on the myocardium¹⁵ were made constituted the source of material for these histologic studies of the brain and spinal cord. Therefore, we need not review the details of the general experimental procedures.

It is necessary, however, to discuss the methods employed in studying the cellular structure of the central nervous system of these experimental animals. As we stated in a previous paper,¹⁵ the cats were killed at various intervals after the administration of different doses of digitalis by placing the animals in an ether or chloroform chamber. The brain and spinal cord were removed as rapidly as possible. The entire brain was immersed in a 10 per cent solution of formalin for forty-eight hours; then small blocks of tissue were removed from the following regions: the left frontal cortex, the left motor cortex, the left visual cortex, the pons, and the cerebellum. These blocks of brain tissue were again immersed in a 10 per cent solution of formalin, and allowed to remain for forty-eight hours or more before they were sectioned and finally stained with cresyl violet. Small blocks of the cervical, thoracic, and lumbar portions of the spinal cord were treated similarly.

Care was taken not to use the brain of any animal on which necropsy was not performed immediately after the animal died or was killed. As a rule, only a few minutes elapsed from the time the animal died until the brain was in a 10 per cent solution of formalin.

The brains and spinal cords of twenty control cats were prepared and studied in a manner similar to that described for the experimental animals.

RESULTS

A. Histologic Studies on the Brain and Spinal Cord of the Control Animals.—The twenty control animals seemed to be in good health before they were killed. No macroscopic abnormalities were observed in the brain or spinal cord of any of them. Microscopic studies of the frontal, motor, and visual cortex revealed scattered, occasional, small pyramidal cells which appeared to be degenerating. There were, how-

ever, no zones of obvious necrosis and extensive degeneration such as were seen in some of the animals which received digitalis. No degenerative changes were observed in the larger pyramidal cells of the cerebral cortex. No evidence of cellular degeneration was seen in the cerebellum, pons, or spinal cord. The blood vessels of the central nervous system seemed to be free from histologic evidence of arteriosclerosis.

B. Histologic Studies on the Brain and Spinal Cord of Animals Which Had Received Calculated Therapeutic Doses of Digitalis.—Two types of experiments were designed to ascertain the effects of calculated therapeutic doses of digitalis on the cellular structure of the central nervous system. To one group of animals (Group A), the calculated therapeutic amount of the drug was administered in a single dose within a period of two to three minutes, or it was given in divided doses over a period of twenty-four to forty-eight hours. The brain and spinal cord were examined microscopically from six to fifty-six days after the drug had been administered. To the other group of animals (Group B), the calculated therapeutic dose of digitalis was administered as in Group A, but, in addition, an estimated daily maintenance dose of the drug was given to the animals over a period of nineteen to sixty days. The daily maintenance dose for the cat was estimated on the basis of body weight to correspond to 1 or 2 cat units for a man weighing 70 kg.¹⁵ The brain and spinal cord of the animals in Group B also were examined histologically nineteen to sixty days after the administration of the digitalis had been started.

TABLE I

CALCULATED THERAPEUTIC DOSES OF DIGITALIS AND DURATION OF THE EXPERIMENT
GROUP A

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Lanatoside A	20	Single dose, intravenous	14
Digalen	30	Single dose, intravenous	6
Lanatoside C	30	Single dose, intravenous	11
Digitoxin	30	Single dose, intravenous	11
Lanatoside A	30	Single dose, intravenous	12
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12
Lanatoside A	30	Divided doses (48 hr.), intravenous	12
Digalen	30	Single dose, intravenous	14
Digitoxin	30	Single dose, intravenous	14
Lanatoside A	30	Single dose, intravenous	18
Lanatoside A	30	Single dose, intravenous	21
Digifortis	30	Single dose, oral	56

In Group A there were twelve cats (Table I). No anatomic changes were found in the brain and spinal cord of any of the animals which had received calculated therapeutic amounts of digitalis, either in single or divided doses.

In Group B there were eleven cats (Table II). The object of the experiments in this group was to ascertain whether demonstrable mor-

TABLE II

DAILY ADMINISTRATION OF THE EQUIVALENT OF 1 OR 2 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED PREVIOUSLY WITH 30 PER CENT OF MINIMAL LETHAL DOSE.

GROUP B

DRUG USED	EQUIVALENT DAILY DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Digalen	1	Intravenous	19
Digifortis	1	Oral	19
Digifortis	1	Oral	30
Digalen	1	Intravenous	34
Lanatoside A	1	Intravenous	36
Digiglusin	2	Intravenous	20
Digifortis	2	Oral	30
Digalen	2	Intravenous	30
Lanatoside A	2	Intravenous	36
Digalen	2	Intravenous	40
Digifortis	2	Oral	60

phologic changes would develop in the central nervous system of digitalized animals which received daily maintenance doses of the drug within the range of doses used in man. Five of the animals which were digitalized with calculated therapeutic doses of digitalis (30 per cent of the minimal lethal dose) received daily maintenance doses that were estimated to be approximately equivalent, on the basis of the body weight of the cat, to 1 cat unit daily for a man weighing 70 kg. The remaining six animals were also digitalized with 30 per cent of the minimal lethal dose of the drug, and then given daily the estimated equivalent of 2 cat units. The body weight of the cat and that of a 70-kilogram man were again used as the basis for the calculations.

No definite cellular changes developed in the brain or spinal cord of any of the animals in Group B, even when the drug was administered daily for two months.

Drowsiness or other recognizable signs of disturbance of the central nervous system were not observed in any of the cats in Group A or B.

C. Histologic Studies on the Brain and Spinal Cord of Animals Which Had Received Toxic Doses of Digitalis. (a) Observations correlating dosage, duration of experiment, and histologic studies—As has been stated elsewhere,¹⁵ grouping the animals in this series was difficult, for the number of animals was rather large, and the manner in which the different digitalis bodies were administered varied considerably. In order to simplify the presentation, the animals were arranged in two major groups: (1) Group A₁, those animals which received single toxic doses of digitalis and subsequently had the brain and spinal cord examined microscopically after various periods; (2) Group B₁, those animals which received multiple doses of digitalis in various toxic amounts over different periods and then had their central nervous systems subjected to histologic study.

Table III shows the amounts of the various single doses of digitalis bodies, the route of administration, the duration of the experiment after

TABLE III

CORRELATION OF SINGLE TOXIC DOSE OF DIGITALIS, DURATION OF THE EXPERIMENT,
AND HISTOLOGIC STUDY OF THE CENTRAL NERVOUS SYSTEM

GROUP A,

DRUG USED	DOSE, PER CENT OF MINI- MAL LETHAL DOSE	METHOD OF ADMINISTRA- TION	DURATION OF EXPERI- MENT	HISTOLOGIC CHANGES			
				CEREBRUM	CERE- BELLUM	PONS	SPINAL CORD
Digalen	40	Intravenous	12 days	No	No	No	No
Digiglusin	40	Intravenous	12 days	No	No	No	No
Lanatoside A	40	Intravenous	12 days	-	-	-	-
Lanatoside C	50	Intravenous	11 days	No	No	No	No
Digitoxin	50	Intravenous	13 days	No	No	No	No
Lanatoside A	50	Intravenous	14 days	No	No	No	No
Digalen	50	Intravenous	15 days	No	No	No	No
Digitoxin	60	Intravenous	12 hours	-	-	-	-
Lanatoside C	60	Intravenous	9 days	No	No	No	No
Lanatoside A	60	Intravenous	10 days	No	No	No	No
Digitoxin	60	Intravenous	10 days	Yes	Yes	No	-
Lanatoside C	60	Intravenous	11 days	Yes	Yes	No	No
Digiglusin	60	Intravenous	12 days	No	No	No	No
Digalen	60	Intravenous	14 days	No	No	No	No
Digalen	60	Intravenous	15 days	No	No	No	No
Lanatoside A	60	Intravenous	15 days	No	No	No	No
Digitoxin	70	Intravenous	4 days	No	No	No	No
Lanatoside C	70	Intravenous	11 days	No	No	No	No
Digiglusin	70	Intravenous	12 days	Yes	Yes	No	No
Digiglusin	75	Intravenous	3 days	No	No	No	No
Digiglusin	75	Intravenous	9 days	-	-	-	-
Lanatoside A	75	Intravenous	12 days	Yes	Yes	Yes	Yes
Digiglusin	80	Intravenous	39 min.	-	-	-	-
Lanatoside A	80	Intravenous	3 hours	-	-	-	-
Lanatoside A	80	Intravenous	4 hours	-	-	-	-
Lanatoside A	80	Intravenous	6½ hours	-	-	-	-
Digalen	80	Intravenous	1 day	No	No	No	No
Lanatoside A	80	Intravenous	2 days	-	-	-	-
Lanatoside A	80	Intravenous	3 days	No	No	No	No
Digalen	80	Intravenous	4 days	No	No	No	No
Lanatoside A	80	Intravenous	5 days	No	No	No	No
Digitoxin	80	Intravenous	6 days	Yes	Yes	Yes	Yes
Lanatoside A	80	Intravenous	7 days	No	No	No	No
Lanatoside A	80	Intravenous	8 days	Yes	Yes	Yes	Yes
Lanatoside C	80	Intravenous	9 days	No	No	No	No
Lanatoside A	80	Intravenous	10 days	No	No	No	No
Lanatoside A	80	Intravenous	10 days	No	No	No	No
Lanatoside C	80	Intravenous	11 days	No	No	No	No
Lanatoside A	80	Intravenous	12 days	Yes + + +	Yes + +	Yes +	± ?
Digalen	80	Intravenous	12 days	-	-	-	-
Digiglusin	80	Intravenous	12 days	?	No	No	No
Lanatoside B	80	Intravenous	12 days	Yes + + + +	Yes + +	Yes + +	Yes +
Digitoxin	80	Intravenous	12 days	-	-	-	-
Tincture digitalis	80	Intravenous	12 days	No	No	No	No
Digifortis	80	Oral	13 days	?	No	No	No
Lanatoside A	80	Intravenous	14 days	No	No	No	-
Digalen	80	Intravenous	14 days	No	No	No	No
Lanatoside A	80	Intravenous	16 days	Yes	Yes	Yes	No
Digalen	80	Intravenous	17 days	Yes	Yes	-	-
Lanatoside A	80	Intravenous	21 days	No	No	No	No
Lanatoside A	80	Intravenous	23 days	Yes	Yes	Yes	Yes
Digalen	80	Intravenous	24 days	Yes	Yes	Yes	Yes
Digalen	80	Intravenous	30 days	No?	No	No	No
Lanatoside A	80	Intravenous	30 days	No?	-	-	-
Digalen	80	Intravenous	42 days	No?	No	No	-
Digalen	80	Intravenous	60 days	No	No	No	No

the drug was administered, and the results of the histologic examination of several parts of the central nervous system. The data summarized in this table indicate the following:

1. No significant anatomic changes were observed in the brain and spinal cord after the administration of either 40 or 50 per cent of the minimal lethal dose.

2. Cellular changes were observed in the cerebral cortex and in the cerebellum in two of eight cats which had received 60 per cent of the minimal lethal dose.

3. When the dose was raised to 70, 75, or 80 per cent of the minimal lethal dose, the frequency of cellular changes increased.

4. Regardless of the size of any single dose of the drug, no definite cerebral lesions were seen during the first five days.

5. When histologic changes occurred after the administration of single doses of digitalis, they were almost always present between the sixth and the twelfth day.

6. The cellular changes in the central nervous system were produced by digitalis whole leaf or crystalline products of digitalis (digitoxin, lanatoside A, B, and C).

7. Lesions did not develop in the brains of all the animals which received toxic doses of digitalis, even when the duration of the experiment was six days or more (that is, within the period during which lesions are producible).

Although it is interesting to know the minimal amount of digitalis which will produce degenerative changes in the central nervous system when the drug is given in a single dose, it is more important from the standpoint of clinical application to ascertain the minimal amount which will cause damage of the nerve cells when the drug is administered daily over a given period, as in treating patients. With this idea in mind, a series of animals was digitalized with 30 per cent of the minimal lethal dose and then subjected to estimated daily doses of digitalis within the toxic range. These daily doses were estimated in the manner described in a previous paper;¹⁵ instead of administering the daily equivalent of 1 or 2 cat units, the animals were given daily amounts corresponding to 3, 4, 5.5, or 6 cat units (let it be recalled again that the body weight of the cat and that of a 70-kilogram man were used as the basis for these calculations).

Table IV summarizes the relation between these various daily toxic doses of digitalis, administered over different periods, and the histologic studies of the brain and spinal cord. The following observations are indicated in Table IV:

1. Definite evidence of cellular degeneration was observed in the central nervous system of seven of eleven animals. In one animal the changes were not very prominent. In three cats no distinct cerebral, cerebellar, pontine, or spinal cord lesions were observed.

2. Three animals were found dead. Their central nervous systems

TABLE IV

CORRELATION OF THE HISTOLOGIC STUDIES OF THE CENTRAL NERVOUS SYSTEM, THE DURATION OF THE EXPERIMENT, AND THE DAILY ADMINISTRATION OF THE EQUIVALENT OF 3, 4, 5.5, OR 6 CAT. UNITS OF DIGITALIS TO CATS DIGITALIZED WITH 30 PER CENT OF THE MINIMAL LETHAL DOSE

GROUP B₁

DRUG USED	DAILY EQUIVALENT DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	HISTOLOGIC CHANGES			
				CEREBRUM	CEREBELLUM	PONS	SPINAL CORD
Digitoxin	3	Intravenous	5	Yes	Yes	Yes	Yes
Digifortis	3	Oral	11	—	—	—	—
Tincture digitalis	3	Intravenous	13	—	—	—	—
Tincture digitalis	3	Intravenous	14	No	No	No	No
Tincture digitalis	3	Intravenous	18	No	No	No	No
Lanatoside A	3	Intravenous	25	Yes	Yes	?	?
Lanatoside A	3	Intravenous	25	Yes	Yes	Yes	Yes
Lanatoside C	3	Intravenous	30	No	No	No	—
Digiglusin	4	Intravenous	7	Yes	Yes	No	No
Digifortis	4	Oral	14	—	—	—	—
Digifortis	4	Oral	19	Yes	Yes	Yes	Yes
Digifortis	4	Oral	30	Yes	Yes	Yes	—
Lanatoside A	5.5	Intravenous	30	Yes	Yes	Yes	Yes
Digifortis	6	Oral	30	Yes	Yes	Yes	—

were not removed for microscopic examination, for we did not wish to have our studies confused by uncontrolled post-mortem changes.

(b) Cellular changes observed in the central nervous system after the injection of toxic doses of digitalis.—It should be recalled that calculated therapeutic doses of digitalis did not produce any significant anatomic changes in the central nervous system.

Toxic doses of digitalis, as indicated in Tables III and IV, did produce degenerative changes in the central nervous system. The extensiveness and intensity of the cellular changes varied with the amount of digitalis, the manner in which it was administered, and the age of the animal. As a rule, the higher the dose of digitalis, the greater was the histologic change in the central nervous system. This observation, however, was modified chiefly by two factors: (1) the lesions were more extensive after the administration of repeated doses of digitalis in the toxic range than after the administration of single toxic doses; (2) the older the animal, the more likely one was to observe cellular changes in the brain.

The frequency and intensity of the cellular changes varied in different parts of the central nervous system. Lesions were most likely to be found in the cerebral cortex, and least likely to be observed in the spinal cord. Although the degenerative changes were extensive in the cerebral cortex at times, they were never very prominent in the spinal cord. The Purkinje cells in the cerebellum showed evidence of degen-

eration when cortical lesions were prominent. The frequency of cellular degeneration in the pons was greater than in the spinal cord, but it was definitely less than in the cerebral cortex.

The cortical degenerative changes tended to occur in small groups of cells. Groups of degenerating pyramidal cells (large and small) were frequently surrounded by anatomically normal cells. This may have some significance when one considers the manner in which the arterial branches from the meninges supply limited zones of cortical tissue. Campbell¹⁶ has adequately described this distribution of the cortical blood supply in the cat. At times the cortical lesions were extensive, and the degeneration involved the majority of the cells. Animals which showed these extensive and advanced lesions of the central nervous system were obviously ill (drowsy, anorectic, spastic, and so forth).

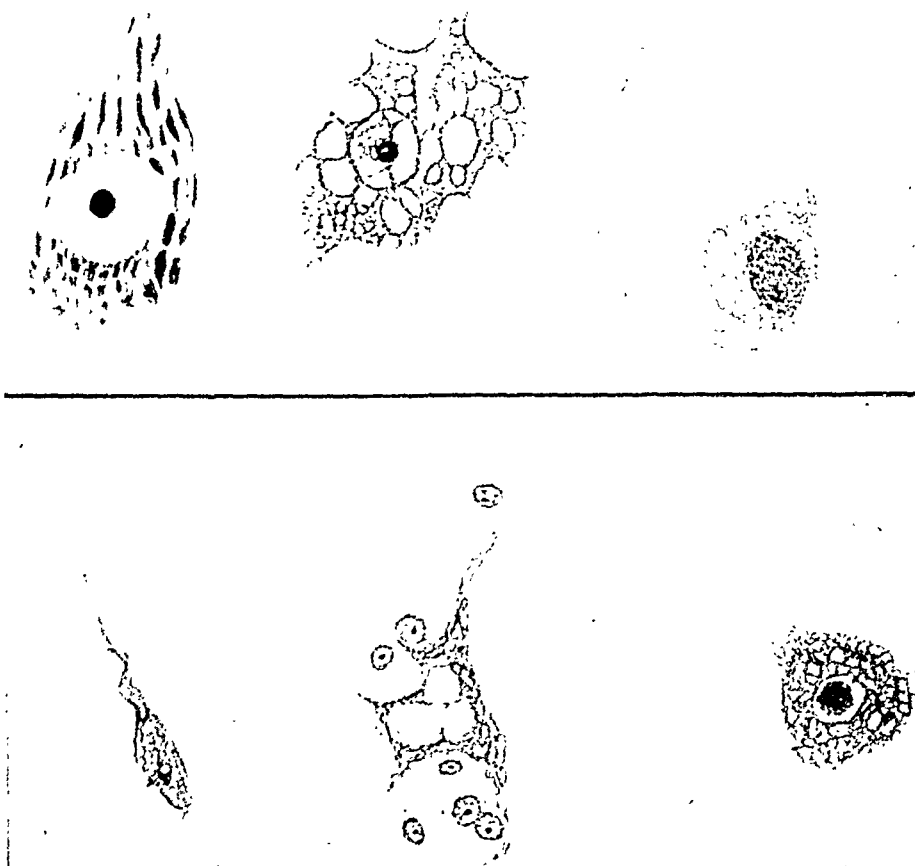


Fig. 1.—Drawing of nerve cells from the cat. Top row, left: normal pyramidal cell from cortex; top row, center: vacuolization in cortical pyramidal cell; top row, right: advanced degeneration in cortical pyramidal cell; bottom row, left: pyknosis in cortical pyramidal cell; bottom row, center: satellitosis in cortical pyramidal cell; bottom row, right: degeneration in cerebellar Purkinje cell.

The following types of significant and definite changes were noted in the cerebral cortex after toxic doses of digitalis had been given:

1. Swollen cells. The pyramidal cells became enlarged; the normal concave contours between the individual processes were replaced by less concave contours or by convex outlines; the cytoplasm usually accepted the stain poorly.

2. Vacuolization. The cytoplasm became rather obviously filled with vacuoles (Fig. 1). These replaced the tigroid Nissl substance of the normal pyramidal cell (Figs. 1 and 2).

3. Degeneration. The cytoplasm underwent vacuolization, degeneration, and, finally, liquefaction. When the cytoplasm of the cell had been completely liquefied, one saw only a ghost area in the cortex in which the cell had once been located. Fig. 1 illustrates one of the stages in this process of degeneration.

4. Pyknosis. The cytoplasm shrank and stained more or less uniformly and deeply with cresyl violet (Fig. 1).

5. Satellitosis. The degenerating pyramidal cell was surrounded by small oligodendroglial cells (Fig. 1).

There was nothing specific about the character of these cellular changes. They have been described by many authors in various anoxic conditions (see literature in the sixth paper of this series).¹⁷

Degenerative changes were seen also in the Purkinje cells of the cerebellum. Fig. 1 shows a Purkinje cell which was undergoing degenerative change.

Similar degenerative changes occurred in the neurons of the pons and the spinal cord, but the lesions were not striking or extensive. Of the portions of the central nervous system which were examined, the cerebral cortex (Fig. 3) was the most vulnerable to toxic doses of digitalis.

If the animal did not die from the toxic dose or doses of digitalis, it recovered completely. It was difficult to recognize anatomic changes in the brains of the animals thirty to sixty days after they had received a toxic dose of digitalis and had recovered.

(c) The factor of age in the production of cerebral lesions.—As in the case of the myocardial lesions,¹⁵ the older animals were more prone than the younger ones to manifest degenerative changes in the pyramidal cells of the cerebral cortex after they had been given toxic doses of digitalis. This difference in the reaction to digitalis could not be accounted for by arteriosclerosis in the older animals, for no evidence of this disease was found in either the arteries or the arterioles of any of the experimental animals.

(d) Observations on signs of intoxication of the central nervous system in cats treated with digitalis.—Drowsiness and, at times, ataxia, with spastic reflexes, were noted in some of the animals from the fifth to the fourteenth day. Several animals died of respiratory failure, which had been preceded by Cheyne-Stokes respiration. If the digitalis

did not cause death by respiratory failure or cardiac failure, the animals recovered, and, to all intents and purposes, were normal.

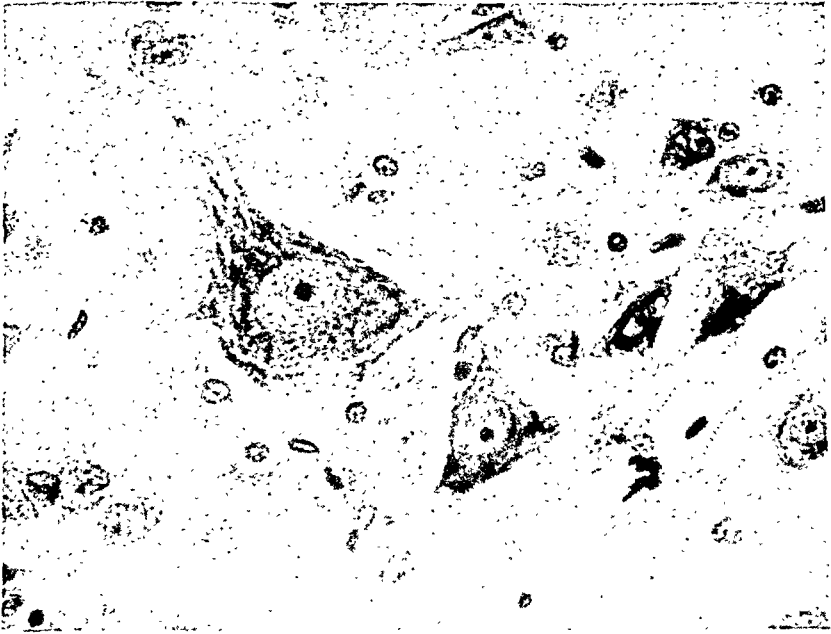


Fig. 2.—Normal pyramidal cell in the motor cortex of control cat. Note the distribution of the Nissl substance ($\times 450$).

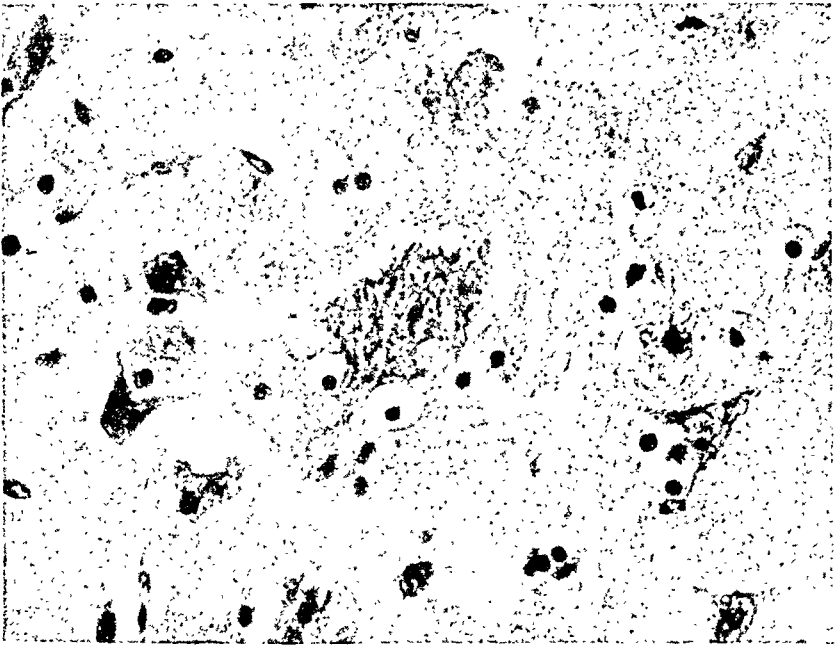


Fig. 3.—Advanced degeneration of the pyramidal cells of the motor cortex twelve days after the injection of a toxic dose of digitalis (75 per cent of the minimal lethal dose of lanatoside A). The animal was drowsy and exhibited spastic reflexes before it was killed ($\times 450$).

SUMMARY

No significant cellular changes were observed in the brain and spinal cord after the administration of calculated therapeutic amounts of digitalis (30 per cent of the minimal lethal dose) in single or in divided doses. The histologic studies were made after a minimum of six days and a maximum of fifty-six days.

No cellular changes were produced in our experimental animals when they were digitalized rapidly with a calculated therapeutic dose of digitalis and then were given maintenance doses of the drug which were estimated to correspond to either 1 or 2 cat units for a man weighing 70 kg. The histologic studies were made after a minimum of nineteen days and a maximum of sixty days.

In our experiments, 60 per cent of the minimal lethal dose was the smallest amount which, when given as a single dose, produced definite evidence of cellular degeneration in the cerebral cortex. This dose of digitalis was in the toxic range.

The frequency with which lesions of the central nervous system occurred increased as the size of the single dose of digitalis was increased to 80 per cent of the minimal lethal dose.

Cerebral lesions were not observed until six or more days after single toxic doses of digitalis had been administered.

Histologic changes were not observed in the central nervous systems of all of the animals which had received toxic amounts of digitalis, even when the quantity of the drug was 80 per cent of the minimal lethal dose.

Degenerative changes were produced in the central nervous system when the animals were digitalized rapidly with a calculated therapeutic dose of digitalis and then were given daily quantities of the drug which were estimated to correspond to 3, 4, 5.5 or 6 cat units for a man weighing 70 kg. The equivalent of 3 cat units daily of parenterally administered digitoxin caused lesions in the brain and spinal cord within five days in one animal, and a corresponding daily dose of orally administered tincture of digitalis produced cellular changes in the central nervous system within eleven days in one animal. The central nervous systems of the digitalized animals in the group which had received daily doses of digitalis in the toxic range were examined microscopically after a minimum of five days and a maximum of thirty days.

The cellular changes in the brain after the administration of digitalis were not specific. The following cellular alterations were observed in the large and small pyramidal cells of the cerebral cortex: swelling of the cell body; vacuolization of the cytoplasm; varying grades of cytoplasmic and nuclear degeneration, up to complete liquefaction of the cell; pyknosis of the cells; and cellular degeneration plus satellitosis.

The cerebral changes often occurred in localized zones, with normal cortical cells in the surrounding tissue. The lesions were at times diffuse when large doses of digitalis had been administered.

Old animals were more prone than young ones to manifest cerebral lesions after the administration of digitalis. This difference of sensitivity to the drug was not related to arteriosclerosis; at least no evidence of this disease was observed in any of the arteries or the arterioles of the central nervous system.

Drowsiness and spastic reflexes were observed in the animals which were markedly intoxicated with digitalis.

Animals which survived the administration of the toxic doses of digitalis recovered completely in three to four weeks.

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THE EFFECTS OF DIGITALIS, URGININ, CONGESTIVE CARDIAC FAILURE, AND ATROPINE ON THE HYPERACTIVE CAROTID SINUS

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ALTHOUGH studies on the carotid sinus reflex¹⁻⁵ in animals and man have established that the activity of the reflex is increased by congestive cardiac failure or by digitalis, little is known of the relative influence of these two factors.

Weiss, Baker, Capps, and Ferris^{6, 7} and Nathanson⁸ have demonstrated that syncopal states produced by pressure over the carotid sinus simulate the spontaneous syncope which affects patients with a hyperactive carotid sinus reflex. In these and other studies it has been shown that the cardiac responses to carotid sinus stimulation can be controlled either by epinephrine (and related compounds) or by atropine. Since coronary disease and arterial hypertension are likely to be associated with hyperactivity of the carotid sinus reflex,^{9, 10} epinephrine may be contraindicated,^{11, 12, 13} whereas moderate doses of atropine are well tolerated by such patients. However, the effect of atropine on a reflex arc which includes the vagus as an efferent pathway is complex. In 1880, Anrep,¹⁴ and, in 1891, Mueller¹⁵ demonstrated that the initial action of atropine was to slow the pulse rate and the late effect was to accelerate it. Petzetakis,¹⁶ in a study of the oculocardiac reflex, demonstrated that the early effect of atropine was to accentuate the slowing of the heart produced by pressure over the eyes. The late effect of atropine tended to abolish the reflex slowing of the heart. He concluded that the early effect of atropine was "due to an increase in the excitability of the cardiomodulator elements contained in the vagi." The late effect of atropine on the oculocardiac reflex was the result of paresis of the vagal endings. These observations have been corroborated and elaborated by numerous investigations.¹⁷⁻²¹ In all reports of the effect of atropine on stimulation of the carotid sinus, only the paralyzing properties of atropine have been considered.

We have studied certain modifications produced by therapeutic doses of atropine on the results of stimulation of the hyperactive carotid sinus reflex. In addition, we have observed the relative effects of digitalis, urginin, and congestive cardiac failure on stimulation of the carotid sinus. Urganin was used to ascertain whether another cardiotonic drug would have effects similar to those of digitalis.

From the Medical Service of St. Luke's Hospital.
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MATERIAL

A group of eight patients who complained of recurring syncope or severe faintness were selected. Previous observations had shown that the cerebral symptoms of these patients were reproduced by pressure at the bifurcation of one or both of the carotid arteries. An associated ventricular pause was usually produced. In one patient such effects were abolished by local anesthesia and subsequent denervation of the sinuses.

Most of the patients had congestive cardiac failure, with or without angina pectoris.

PROCEDURE

At suitable intervals the above patients were seated in a comfortable chair and the heart rate was obtained by an electrocardiographic tracing. The carotid sinus was then stimulated by applying pressure at the bifurcations of the carotid arteries, and the activity of the sinus reflex was ascertained by the slowing of the ventricular rate produced by such pressure. When stimulation of the sinus resulted in slowing of the ventricles, "R-R-intervals" were measured. Such intervals represent the average duration of the ventricular complexes which occurred during a constant period of stimulation. If stimulation of the carotid sinus made an R-R interval longer than 3.6 seconds, the actual duration of the pause was recorded, and no average value was taken.

To avoid variations in stimulation, firm pressure was made with three fingers over the bifurcations of the carotid arteries, and the sinuses were vigorously massaged. Pressure was usually maintained for more than fourteen seconds. Occasionally this interval had to be shortened because the patient's necks became tender from the vigorous massaging. Repeated stimulations were separated by ten-minute rest periods, for bizarre results occasionally occurred when pressure was made at shorter intervals. The pressure points were intentionally shifted, and the maximum effect obtained from three periods of stimulation was used for comparative purposes. In the prolonged atropine experiments the pressure points were constant after the initial control periods.

The carotid sinuses of two patients were in close approximation to the larynx, and pressure occasionally caused marked coughing; in one case the carotid artery was so large and tortuous that it was sometimes difficult to maintain sustained massage of the artery. The results obtained from such unsatisfactory stimulation were discarded. In two cases the less sensitive side was selected for study, but a fairly marked response was generally obtained except in the case of A. G., who previously had had a bilateral stripping operation upon the carotid arteries.

Digitalis was used in 0.1 Gm. pills, made from a standard powdered leaf. Uarginin was used in 0.5 mg. oral tablets. The effects of uarginin on congestive cardiac failure and the electrocardiogram have been adequately reviewed.^{22,23} Equivalent therapeutic doses of these drugs were taken in small quantities until changes in the electrocardiograms were observed or minor toxic manifestations had occurred. The electrocardiographic indications of digitalis activity in our cases were greatly restricted, for slowing of the heart and changes in conduction intervals might occur because of the hyperactive carotid sinus reflex. Changes in the electrocardiograms are indicated in Table I by the sign "?" when they did not seem to be chiefly caused by the cardiotonic drugs. The drugs were continued in maintenance amounts until their influence on the carotid sinus could be ascertained. Occasionally, larger quantities of the drugs were used initially, but, in such rare instances, small doses were taken for a minimum of forty-eight hours preceding sinus massage. The infrequent departures from the standard method of administration were necessary to relieve myocardial failure. One glucoside was usually discontinued for at least three weeks before the second was started.

TABLE I

DAILY MAINTENANCE DOSE OF THE CARDIOTONIC DRUGS AND RESULTING
ELECTROCARDIOGRAPHIC CHANGES

DATE	DAILY R	EKG CHANGES
<i>Case 1 (R. McA.)</i>		
11/ 2/38	Urg. 1.5 mg.	Moderate S-T I, II, III
2/23/39	Urg. 1.5 mg.	Slight S-T I, II, III
4/ 6/39	Dig. 0.1 Gm.	Marked S-T I, II, III
1/30/40	Dig. 0.3 Gm.	Marked S-T I, II, III
2/ 3/40	Dig. 0.3 Gm.	Marked S-T I, II, III
2/17/40	Dig. 0.2 Gm.	Marked S-T I, II, III
<i>Case 2. (F. S.)</i>		
8/26/38	Dig. 0.15 Gm.	Moderate S-T I, II, III
10/ 8/38	Urg. 1.5 mg.	Moderate S-T I, II
12/10/38	Urg. 1.5 mg.	Moderate S-T I, II, III
5/ 1/39	Dig. 0.2 Gm.	Moderate S-T I, II, III
6/19/39	Dig. 0.2 Gm.	Moderate S-T I, II
7/10/39	Dig. 0.2 Gm.	Moderate S-T II*
9/ 9/39	Dig. 0.2 Gm.	Moderate S-T I, II
4/11/40	Urg. 1.5 mg.	Moderate S-T I, II
4/27/40	Urg. 1.0 mg.	Moderate S-T I, II
6/10/40	Dig. 0.15 Gm.	Moderate S-T I, II
9/11/40	Dig. 0.15 Gm.	Moderate S-T I, II
11/30/40	Dig. 0.15 Gm.	Moderate S-T I, II
3/26/41	Urg. 2.0 mg.	Moderate S-T I, II
7/12/41	Dig. 0.15 Gm.	Moderate S-T I, II
<i>Case 3. (A. G.)</i>		
11/28/38	Urg. 2.0 mg.	Moderate S-T I, II, III
12/12/38	Urg. 1.0 mg.	Moderate S-T I, II, III
1/11/39	Urg. 1.0 mg.	Slight S-T I, II
2/ 9/39	Dig. 0.2 Gm.	Slight S-T I, II, III
5/ 8/39	Dig.†	None
7/29/41	Dig. 0.3 Gm.	Marked S-T I, II
<i>Case 4. (H. Z.)</i>		
2/24/39	Dig. 0.2 Gm.	?
5/ 1/39	Dig. 0.3 Gm.	?
6/16/39	Dig. 0.2 Gm.	?
7/17/39	Dig. 0.2 Gm.	?
4/30/41	Urg. 2.0 mg.	?
5/19/41	Urg. 2.0 mg.	?
<i>Case 5. (I. R.)</i>		
12/ 2/38	Urg. 1.5 mg.	?
12/19/38	Urg. 1.5 mg.	?
1/ 5/39	Urg. 1.0 mg.	?
2/ 7/39	Dig. 0.1 Gm.	?

Dig.: Digitalis Folia. Urg.: Uarginin. ? EKG: when electrocardiographic abnormalities were not definitely attributable to the drugs, there were often abnormalities of T and S-T.

*Leads I, III not taken.

†C. S. P. 1 hr. 12 min. after 14 c.c. digalen I.V.

Standard tablets of atropine were dissolved in 1 c.c. of sterile water and injected subcutaneously in the right deltoid region. Doses of 0.0012 Gm. (gr. 1/50) and 0.0018 Gm. (gr. 1/33) were used. These quantities sometimes caused dryness of the mouth and a disturbance in vision which occurred, for the most part, after the periods of observation. The reactions were not so severe as to preclude future cooperation on the part of the patients. Partial paralysis of the vagus was produced slowly enough to allow sufficient time to study the varying effects of atropine.

TABLE II
RESULTS OF ATROPINE OBSERVATIONS IN 5 CASES

CASE	DATE	R	TIME	R-R INT. REST	R-R INT. C.S.P.	DATE	R	TIME	R-R INT. REST	R-R INT. C.S.P.	DATE	R	TIME	R-R INT. REST	R-R INT. C.S.P.
1	2/22/39	Urg. 1.5 mg.	Control	0.72	1.14	2/6/39	None	Control	0.66	1.06	4/6/39	Dig. 0.1 Gm.	Control	0.74	1.43
			—Atr. 5 min.	0.85	1.10			—Atr. 5 min.	0.0012	Gm.—			—Atr. 5 min.	0.0012	Gm.—
2	12/10/38	Urg. 1.0 mg.	9 min.	0.69	0.89	2/17/39	None	15 min.	0.68	1.14	3/28/39	None	14 min.	0.74	1.51
			19 min.	0.52	0.95			28 min.	0.57	1.19			21 min.	0.68	0.93
			29 min.	0.52	0.83			36 min.	0.52	0.81			34 min.	0.61	1.03
			44 min.	0.58	1.18			48 min.	0.53	0.70			45 min.	0.65	0.95
			54 min.	0.62	0.85			55 min.	0.53	0.75			54 min.	0.63	0.91
			64 min.	0.61	1.01				0.56	0.88					
3	12/12/38	Urg. 1.0 mg.	Control	1.05	8.12	1/11/39	Urg. 1.0 mg.	Control	1.00	1.14	2/9/39	Dig. 0.1 Gm.	Control	0.96	11.50
			—Atr. 10 min.	0.0012	Gm.—			—Atr. 5 min.	0.0012	Gm.—			—Atr. 8 min.	0.0012	Gm.—
			20 min.	1.12	11.48			15 min.	1.02	1.61			20 min.	0.98	11.90
			40 min.	0.86	3.70			37 min.	0.96	1.13			31 min.	0.90	6.60
			55 min.	0.81	1.81			50 min.	0.71	0.90			41 min.	0.92	1.60
			70 min.	0.97	2.07			60 min.	0.72	0.91			51 min.	0.77	1.17
4	1/3/39	Urg. 1.5 mg.	Control	0.95	1.48	1/19/39	None	Control	0.75	0.83	2/24/39	Dig. 0.2 Gm.	Control	0.78	1.29
			—Atr. 5 min.	1.40	1.47			—Atr. 5 min.	1.26	1.60			—Atr. 5 min.	1.26	1.63
			10 min.	0.0012	Gm.—			11 min.	0.0018	Gm.—			10 min.	0.0018	Gm.—
			25 min.	1.45	1.70			21 min.	1.30	1.66			26 min.	1.27	1.54
			31 min.	1.41	1.50			31 min.	1.29	1.65			37 min.	1.27	1.46
			41 min.	1.33	1.41			41 min.	1.21	1.37			47 min.	1.20	1.27
5	1/5/39	Urg. 1.0 mg.	Control	1.30	1.37	2/7/39	Dig. 0.1 Gm.	Control	1.05	1.18	2/7/39	Dig. 0.1 Gm.	Control	1.18	1.32
			—Atr. 5 min.	1.28	1.38			—Atr. 6 min.	1.07	1.13			—Atr. 10 min.	1.21	1.30
			11 min.	1.34	1.43			13 min.	1.16	1.21			25 min.	1.22	1.29
			21 min.	1.34	1.40			33 min.	0.70	1.66			35 min.	0.80	3.80
			31 min.	0.70	6.30			43 min.	0.0018	Gm.—			47 min.	0.83	4.82
			41 min.	0.81	4.60			54 min.	0.75	6.70				0.88	1.51
5	1/5/39	Urg. 1.0 mg.	Control	0.87	5.40	2/7/39	Dig. 0.1 Gm.	Control	0.77	1.07	2/7/39	Dig. 0.1 Gm.	Control	0.87	7.46
			—Atr. 5 min.	0.84	3.82			—Atr. 6 min.	0.56	0.75			—Atr. 6 min.	0.0012	Gm.—
			11 min.	0.69	0.83			13 min.	0.52	0.61			12 min.	1.00	8.44
			21 min.	0.66	1.07			23 min.	0.53	0.66			23 min.	1.00	5.72
			31 min.	0.66	0.96			33 min.	0.54	0.70			33 min.	0.91	1.40
			41 min.	0.88	4.42			43 min.	0.51	0.70			33 min.	0.85	2.07
5	1/5/39	Urg. 1.0 mg.	Control	0.77	0.97	2/7/39	Dig. 0.1 Gm.	Control	0.57	0.89	2/7/39	Dig. 0.1 Gm.	Control	0.87	1.17
			—Atr. 7 min.	0.97	7.36			—Atr. 14 min.	0.54	0.70			51 min.	0.87	1.17
5	1/5/39	Urg. 1.0 mg.	14 min.	0.84	1.31	2/7/39	Dig. 0.1 Gm.	12 min.	0.51	0.70	2/7/39	Dig. 0.1 Gm.	58 min.	0.89	1.25
			24 min.	0.77	1.08			23 min.	0.51	0.70					
5	1/5/39	Urg. 1.0 mg.	34 min.	0.76	1.08	2/7/39	Dig. 0.1 Gm.	33 min.	0.51	0.70	2/7/39	Dig. 0.1 Gm.			
			44 min.	0.77	0.97			51 min.	0.51	0.70					
5	1/5/39	Urg. 1.0 mg.	54 min.	0.76	1.14	2/7/39	Dig. 0.1 Gm.	58 min.	0.51	0.70	2/7/39	Dig. 0.1 Gm.			

Atr.: Atropine sulfate subcut. Urg.: Urgidin. Dig.: Digitalis Folia. R-R Int.: average ventricular cycle. C.S.P.: Carotid Sinus Pressure.

The functional classification of the cases was made according to the Standard Nomenclature of The American Heart Association.

RESULTS

The response of the eight patients to carotid sinus stimulation after the administration of atropine was ascertained on twenty-one occasions. The observations on three patients do not appear in Table II because they were unwilling to cooperate throughout the study. On sixteen occasions a transient increase in the response to sinus stimulation was demonstrated. The augmented response was present five to twelve minutes after atropine was injected subcutaneously. No attempt was made to ascertain the time of onset or total duration of this initial stage. There was a variable degree of paresis of the carotid sinus reflex in all of the patients for the remainder of the experimental period, which lasted forty-seven to seventy minutes after the injection. These effects are illustrated in Fig. 1.

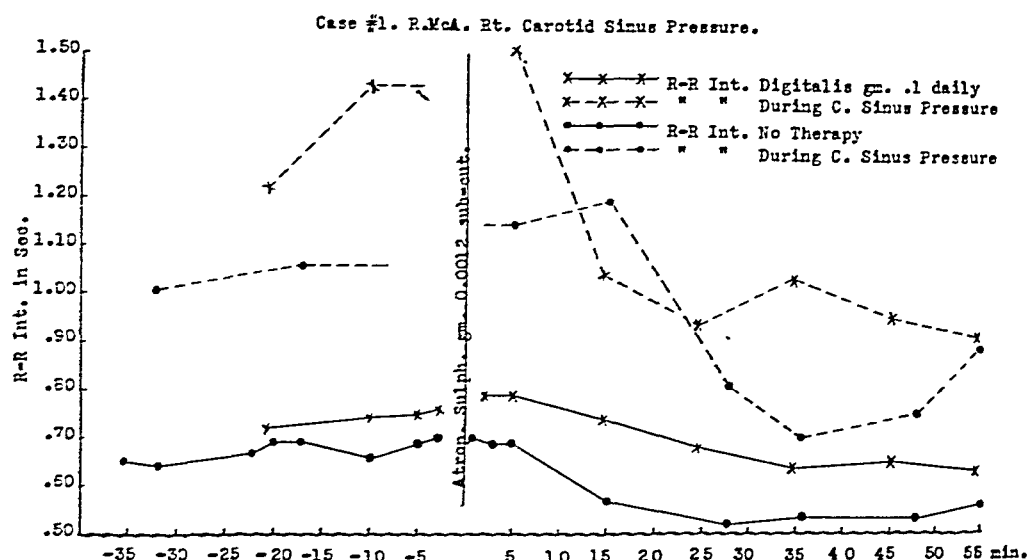


Fig. 1.—Case 1. R. McA. Effect of atropine on the results of carotid sinus pressure. Ordinates: minutes before and after subcut. injection of atropine sulfate. Abscissae: duration of average ventricular cycle in seconds. The upper two curves represent the R-R values with carotid sinus pressure; the lower two curves are the control ventricular rates immediately preceding sinus pressure.

The relative influence of digitalis, urginin, and congestive failure on carotid sinus stimulation was ascertained in the following cases:

Case 1.—R. McA., a white man, 60 years of age, was admitted to St. Luke's Hospital Dec. 16, 1936; he was in acute respiratory distress, and had pink, frothy sputum. Shortness of breath on exertion had been present for the preceding six weeks. He was discharged improved. Thereafter his physical condition was variable; occasionally he was able to do heavy work as a stonemason. Severe dizziness was sometimes present. During this period of relatively good health the standard observations on the results of stimulation of the carotid sinus were begun. The observations were continued throughout subsequent visits, when his circulatory status fluctuated greatly. Moderate congestive failure was precipitated by a mild rhinitis in December, 1939. He was admitted to the hospital Jan. 17, 1940, and discharged

greatly improved on Feb. 3, 1940. Two weeks later he returned with a severe respiratory infection and generalized edema. A pneumococcus (Type XV) was identified in the sputum. Although the pulmonary infection improved as the result of sulfapyridine therapy, the patient died on March 8, 1940, of congestive cardiac failure, with marked azotemia. At post-mortem examination the heart weighed 530 Gm.; there were thickening of the endocardium of the left atrium, mild fibrous changes in the tricuspid valve, and a bicuspid aortic valve, with calcification of the leaflets. The lungs showed moderate pneumoconiosis, with emphysematous blebs and multiple, small infarctions.

The results of stimulating the carotid sinus in Case 1 are illustrated in Fig. 2. On seven occasions the functional classification was I, and, during six of these periods, sinus pressure resulted only in slowing of the ventricles. Myocardial insufficiency was present at the time of the remaining observations, and in all of these ventricular standstill was induced. The patient was taking digitalis on four occasions and urginin on two others, but ventricular standstill was produced by sinus stimulation on only three occasions.

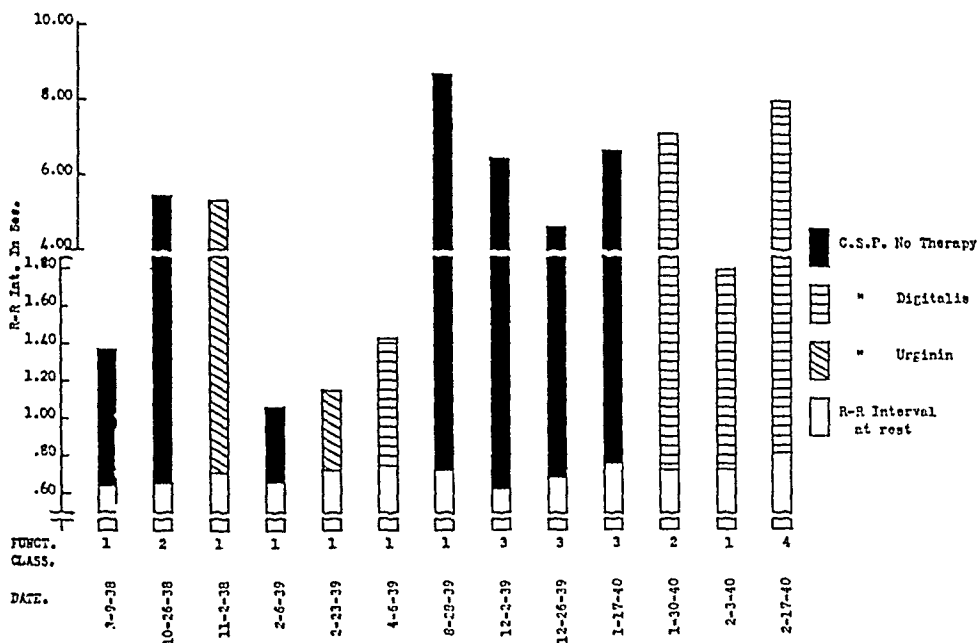


Fig. 2.—Case 1. R. McA. Effect of carotid sinus pressure on the ventricular rate. Abscissae: average ventricular cycle in seconds. FUNCT. CLASS.: functional classification according to American Heart Association. C.S.P.: average R-R intervals with carotid sinus pressure. R-R interval at rest: control ventricular rate immediately preceding carotid sinus stimulation. The symbols in the remaining charts are similar.

The longest period of ventricular standstill occurred Aug. 28, 1939, when the functional classification was I. This result is unexplained. The symptoms produced by carotid sinus pressure showed a marked variation. On Aug. 28, 1939, stimulation resulted in transient syncope, hyperpnea (++), and clonic movements of the arms. On Feb. 17, 1940, when Class IV congestive failure was present, stimulation resulted in opisthotonos with generalized clonic movements (+++), hyperpnea (+++), marked pallor of the skin, a sustained fall in blood pressure, and involuntary micturition. When the patient had acute pulmonary edema, standstill of the heart, with syncope, was produced by slight pressure on the neck.

Case 2.—F. S., a white man, 54 years of age, was seen in the Outpatient Department on Feb. 17, 1937. He was short of breath on exertion, and had occasional attacks of paroxysmal nocturnal orthopnea and swelling of the legs. He had ex-

perienced frequent, severe attacks of dizziness for a year. There was a history of multiple attacks of acute migratory polyarthritis in childhood, and of a penile chancre at the age of 19 years. His blood Wassermann and Kline reactions were strongly positive. Sugar was present in the urine, and a glucose tolerance test showed prolonged hyperglycemia. The diagnoses were rheumatic heart disease, with mitral and aortic stenosis, latent syphilis, and mild diabetes mellitus. The latter condition was controlled by diet and infrequent, small doses of insulin. Adequate antisyphilitic therapy was given, and the standard observations on the carotid sinus reflex were begun on March 12, 1938. His condition has been variable, but the patient has remained cooperative and cheerful, and continues to attempt to be self sufficient. The dizziness is still present, but is less severe than when he was first examined.

Twenty-one observations in Case 2 are recorded in Fig. 3. Arbitrarily, for the purpose of discussion, the carotid sinus was considered to be hyperactive in this case when stimulation of the sinus produced a ventricular pause of more than 7.5 seconds. This occurred fourteen times, and the functional classification on thirteen of these occasions was III. The patient was receiving a cardiotonic drug when fourteen of the observations were made, but on six of these occasions stimulation did not produce ventricular standstill for 7.5 seconds. When the patient was receiving no medication, but was in Class III (six times), sinus massage uniformly produced prolonged standstill of the ventricles. When he was in Class II (eight times), such an effect was secured only once, although he was taking digitalis on seven of these occasions. The carotid sinus reflex in this case was apparently more sensitive when circulatory insufficiency was marked (Class III) than when a therapeutic concentration of either digitalis or uginin was present.

In an attempt to test the above inference, the periods of prolonged ventricular standstill when Class III congestive failure was present were analyzed statistically. The mean of the ventricular pauses when he was receiving no drug was 12.32 seconds, and the mean of the pauses was 11.19 seconds when he was taking digitalis or uginin. The difference of the means is 1.13, and the standard error of the difference is 1.16, so that the difference is not significant.

On Feb. 17, 1939, two trials of carotid sinus pressure resulted in average ventricular cycles of 1.12 and 1.14 seconds. We are reasonably certain that the sinus reflex was not hyperactive on that date. The patient's condition was good at this time and he was taking no drugs.

Case 3.—A. G., a colored man, 66 years of age, was brought to St. Luke's Hospital Dec. 27, 1936, by police ambulance after he had fallen unconscious on the street. There was a long history of repeated syncope, with frequent attacks of severe dizziness, for the preceding three years. The diagnoses were syphilitic aortitis, myocardial hypertrophy with circulatory insufficiency, and carotid sinus syndrome. His respiratory distress diminished after antisyphilitic therapy, but he was usually short of breath after moderate exertion. The syncopal attacks did not recur, but the patient attributed their absence to his physical inactivity. This sedentary life was necessitated by severe dizziness which was precipitated by movements of the neck. Stripping operations on the carotid arteries were done separately in October and November, 1937. A carotid body was histologically identified in material obtained from the right artery. Thereafter he had no recurrence of his "spells," although the ventricular rate was always slowed by pressure over the bifurcation of the right carotid artery. These results were in distinct contrast to those obtained preoperatively, when carotid sinus stimulation, although very slight, usually produced ventricular standstill, with syncope and convulsive movements. The standard observations on the results of carotid sinus stimulation were begun April 9, 1938, and continued to July 29, 1941. During this period there were times when minimal degrees of congestive failure were present.

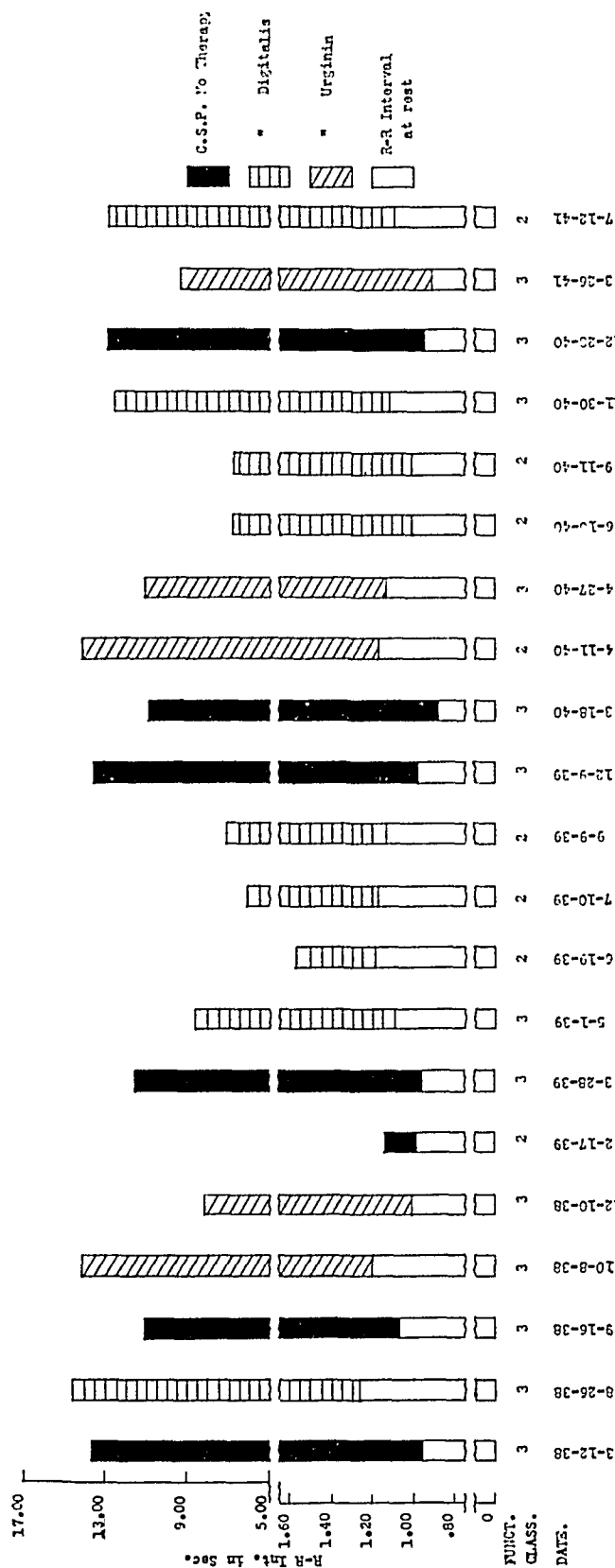


Fig. 3.—Case 2. F. S. Effect of carotid sinus pressure on the ventricular rate. (Symbols as in Fig. 2.)

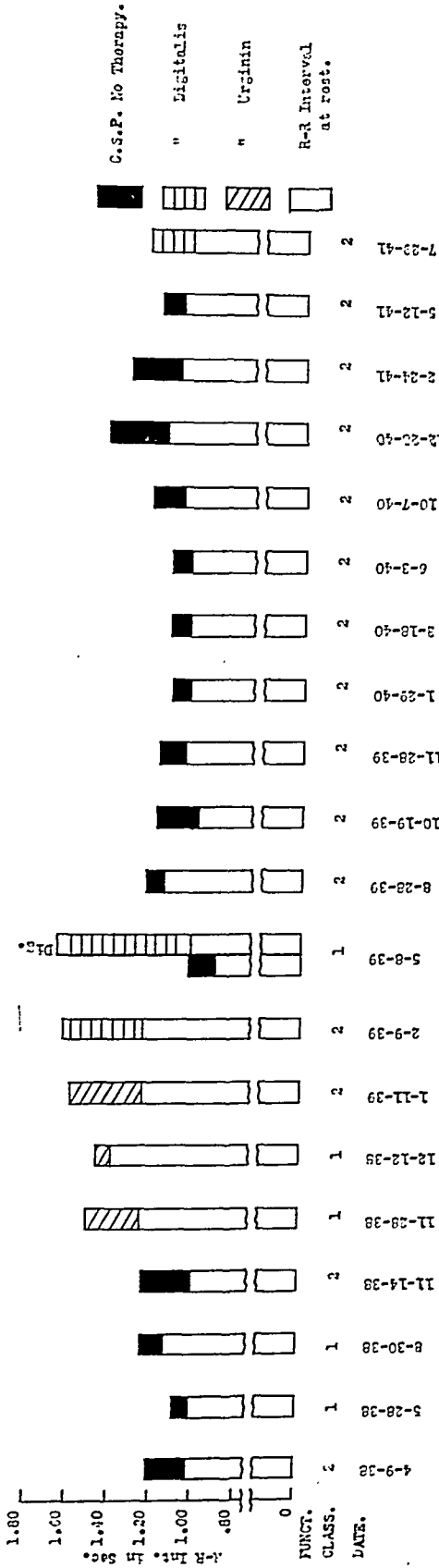


Fig. 1.—Case 3. A. G. Effect of carotid sinus pressure on the ventricular rate. Dig.: 14 c.c. digalen intravenously. (Other symbols as in Fig. 2.)

The average duration of the ventricular cycle after stimulation of the carotid sinus on twenty-one occasions is shown by Fig. 4. The sensitizing effect of digitalis and urginin seems apparent. Statistical analysis of the results shows that the dif-

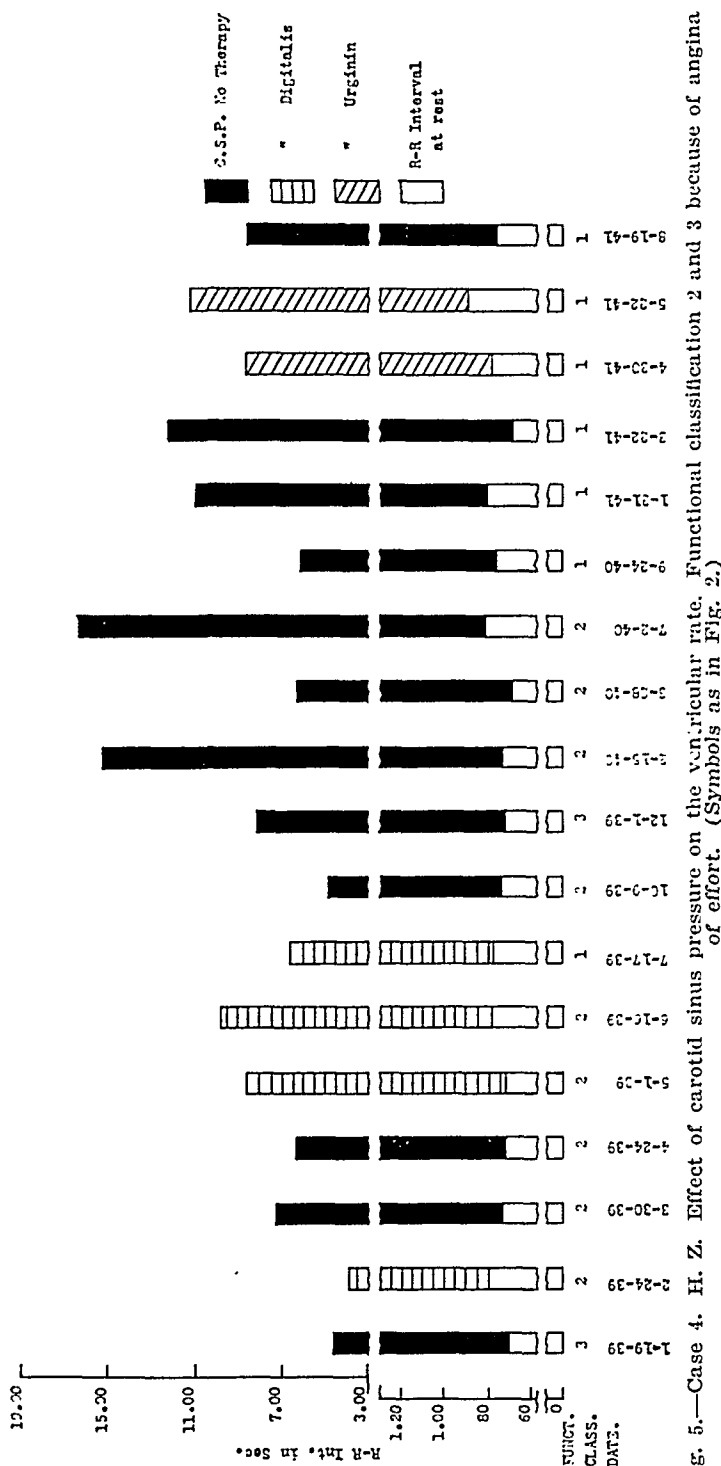


Fig. 5.—Case 4. H. Z. Effect of carotid sinus pressure on the ventricular rate. Functional classification 2 and 3 because of angina of effort. (Symbols as in Fig. 2.)

ference is significant. The mean of six pressures when the patient was receiving digitalis or urginin was 1.51 seconds, and the mean of the control group was 1.20 seconds. The difference of the means is 0.307, and the standard error of the difference is 0.0549.

On May 8, 1939, the maximum ventricular cycle without stimulation was 0.92 second, and during carotid sinus pressure the maximum average cycle was 1.04 seconds. A moderate dose of digalen (14 c.c.) was given intravenously, and seventy-two minutes later the maximum average cycle was 1.03 seconds; with carotid sinus stimulation the average ventricular cycle increased to 1.66 seconds.

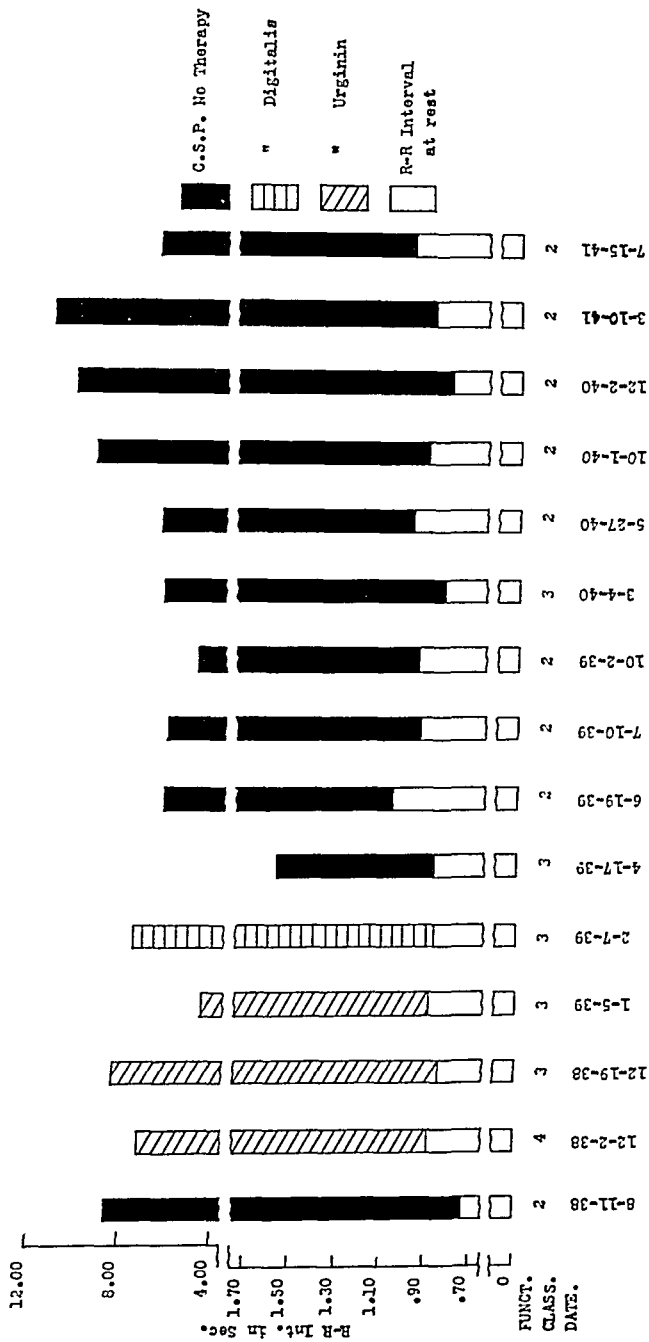


Fig. 6.—Case 5. I. R. Effect of carotid sinus pressure on the ventricular rate. Functional classification 2, 3, and 4 because of angina pectoris. (Symbols as in Fig. 2.)

Case 4.—H. Z., a white man, 44 years of age, was admitted to the hospital July 31, 1937, with severe, persistent precordial pain. He had experienced repeated attacks of dizziness for two years, and had fallen to the floor unconscious on several occasions. The diagnoses were acute myocardial infarction, diabetes mellitus, and carotid sinus syndrome. The carotid sinus was stimulated on numerous occasions, and the standard observations were made between Jan. 19, 1939, and Aug. 19, 1941. The diabetes was of moderate severity, and recurring anginal discomfort

was occasionally present. The only possible evidence of congestive failure was a variation of the breath sounds at the extreme bases of the lungs posteriorly on several occasions.

Fig. 5 shows the cycle lengths during stimulation of the carotid sinus on eighteen separate occasions. On four occasions the patient was receiving digitalis, and, on two others, urginin, but there is no evidence that the carotid sinus had been sensitized by either of these drugs. The variability of the results is noteworthy, although the carotid sinus was extremely hyperactive on several occasions.

Case 5.—I. R., a white man, 54 years of age, was admitted to the hospital Nov. 20, 1937, because of acute myocardial infarction complicated by pulmonary infarction. He was discharged Nov. 13, 1938, and remained under observation thereafter. His general condition has been satisfactory, although his activities have been restricted because of respiratory distress and attacks of angina pectoris. A few spontaneous syncopal attacks have occurred, and attacks of dizziness have been frequent, but not severe.

The effects of carotid sinus pressure on fifteen occasions are shown in Fig. 6. Urginin was given for three periods, and digitalis for one. We are unable to correlate the varying results of sinus stimulation with any of the factors under consideration in the present communication.

An analysis of the data in these five cases showed no apparent difference in the sensitizing effects of digitalis and urginin in small doses (Figs. 2-6). Therefore, we believe that these two drugs, when given in small doses, have relatively the same influence on the hyperactive carotid sinus reflex.

DISCUSSION

The activity of the carotid sinus reflex cannot be absolutely reflected by the change in ventricular rate which results from its stimulation, for the efferent paths of the reflex are complex and show individual variations.^{6, 7} However, ventricular cycles can be accurately measured and control of the heart rate is one of the major functions of the carotid sinus.²⁴ In addition, the ventricular cycles in our cases definitely tended to become longer as the intensity of the induced syncopal states increased.

The results of the atropine experiments seem to be conclusive, and might have been anticipated, for previous reports had clearly indicated their probability. The observations show that the effect of carotid sinus stimulation on the heart rate is first increased and then decreased by the subcutaneous injection of atropine sulfate. The early effect (greater slowing of the heart) seems to be merely an exaggeration of the initial vagotonia which is exhibited by the vagus after the administration of atropine.

Our observations are in accord with previous statements that congestive cardiac failure increases the activity of the carotid sinus. Congestive failure was the only factor in Cases 1 and 2 which was constantly associated with prolonged ventricular standstill and with an increase in severity of symptoms after sinus massage. Therefore, we believe that myocardial insufficiency was the major factor in the carotid sinus syndrome in these two cases. It is improbable that such a change would occur so regularly unless a causal relationship existed. Our observations

indicate that the decrease in the sensitivity of the carotid sinus reflex which results from improvement of the circulation in such cases will exceed any vagotonia produced by small doses of digitalis.

We doubt that digitalis may be responsible for sudden death in patients with a hyperactive carotid sinus reflex. Nevertheless, large doses of this drug result in an increased activity of the carotid sinus reflex before improvement in the circulation occurs. Therefore, we elected to digitalize our patients with small doses,²⁵ and we believe that they received sufficient amounts of the drugs. In Case 1 the dose of digitalis was temporarily increased, with moderate toxic effects, but with no further improvement in the circulation. Although small doses were constantly used in Case 2, mild toxic symptoms were produced occasionally, and the respiratory distress and peripheral edema were greatly alleviated.*

The sensitivity of the carotid sinus reflex was demonstrably increased by small doses of digitalis in Case 3. In this instance, carotid sinus pressure resulted in a slowing of the heart rate after the administration of 0.2 Gm. (gr. iii) of digitalis folia or of 1.0 to 2.0 mg. of Uarginin daily. Increased sensitivity of the sinus was produced promptly in this case by giving a moderate dose (14 c.c.) of digalen intravenously. The results of sinus massage were so variable in Cases 4 and 5 that the sensitizing effect of digitalis was not apparent. Only minor electrocardiographic changes occurred after the administration of digitalis, and congestive failure was never present in these two cases.

Throughout these observations there were occasional, spontaneous variations in the activity of the carotid sinus reflex, and, on one occasion (Case 1), sinus stimulation resulted in unexplained, prolonged ventricular standstill, although the patient was not taking digitalis or uarginin, and the circulation was adequate. We believe that such spontaneous changes had little influence on the results obtained from stimulation of the carotid sinus in our cases.

CONCLUSIONS

In our cases, both congestive cardiac failure and digitalis increased the activity of the carotid sinus reflex, but congestive failure was a more potent factor than small doses of digitalis.

Hyperactivity of the carotid sinus reflex is no contraindication to the use of digitalis in the treatment of congestive cardiac failure.

Digitalis and uarginin, when given in small doses, have similar effects on the hyperactive carotid sinus reflex.

Therapeutic doses of atropine, given subcutaneously, have the following effect on the results of carotid sinus stimulation: after the injection of atropine, stimulation of the carotid sinus will produce a

*The improvement in the circulation in these cases after the use of digitalis is of additional interest. Previous to the administration of digitalis, significant degrees of congestive failure were sometimes present, although the heart rate was slow and the vagus tone was apparently increased. Presumably, this increased vagotonia was sometimes so marked that it resulted in cardiac standstill and syncope. Similar observations have been made previously.²⁵

greater slowing of the heart; this phase of atropine action will be followed by a period of vagal paresis, during which stimulation of the carotid sinus has a lessened effect on the heart rate.

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THE EFFECT OF QUINIDINE UPON SINUS TACHYCARDIA, INCLUDING THE PRODUCTION OF TRANSIENT BUNDLE BRANCH BLOCK

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THE observations to be described in this paper were made in connection with a study of auricular paroxysmal tachycardia. It is well known that quinidine frequently slows the cardiac rate in auricular paroxysmal tachycardia, and sometimes stops the paroxysm. The same effects may be produced by quinine, and the actions of these two drugs are, no doubt, similar. Singer and Winterberg¹ have shown that in sinus tachycardia quinine either does not alter the heart rate or increases it somewhat. It seemed desirable to investigate the effect of quinidine in sinus tachycardia.

A single dose of 0.6 Gm. of quinidine sulfate was given by mouth to each of five patients with sinus tachycardia. Four of the patients had exophthalmic goiter, and the fifth had chronic ulcerative colitis with fever and anemia. In all five cases the heart was organically sound, and none of the patients was receiving any drug which might affect the heart. The heart rate was counted at intervals before, and for at least two hours after, giving the quinidine, and electrocardiograms were likewise taken before giving the quinidine and two hours later.

The effect of quinidine upon the heart rate is shown in Table I. The rate was not affected or was slightly increased. These observations are similar to those of Singer and Winterberg,¹ who used quinine. They show that quinidine does not slow the rate of impulse formation in the sinoauricular node.

The electrocardiograms showed, in some instances, slight changes in the T waves after the administration of quinidine. With one exception, however, there were no significant alterations in the P-R or QRS intervals.

The one exception was Case 5, in which there was transient right bundle branch block two hours after the administration of the quinidine. Electrocardiograms taken a few minutes before the quinidine was given, and again on the following day, were essentially normal (Fig. 1). Multiple precordial leads showed relatively late activation of the right ventricle at the time when the bundle branch block was present. Two weeks later, 0.6 Gm. of quinidine sulfate was again given by mouth,

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TABLE I
THE EFFECT OF QUINIDINE BY MOUTH UPON THE HEART RATE IN SINUS TACHYCARDIA

CASE 1			CASE 2.			CASE 3			CASE 4			CASE 5			
TIME	RATE		TIME	RATE		TIME	RATE		TIME	RATE		TIME	RATE	TIME	RATE
12/15/41			2/ 7/41			3/ 6/41			11/12/41			2/ 7/41		2/21/41	
11:00 a.m.	156		1:00 p.m.	108		4:00 p.m.	120		1:45 p.m.	150		1:00 p.m.	90	1:30 p.m.	108
11:15	147		1:15	110		4:01	Quinidine		2:20	142		1:15	110	1:35	94
2:30 p.m.	Quinidine		1:35	124			0.2 Gm.		2:23	186		1:35	108	1:45	Quinidine
	0.2 Gm.		1:45	112			(test dose)		2:25	Quinidine		1:45	110		0.6 Gm.
	(test dose)		2:15	115		5:00	108			0.6 Gm.		1:55	107	2:45	130
12/16/41			2:20	Quinidine		3/ 7/41			3:00	140		2:00	Quinidine	3:45	130
9:20 a.m.	143			0.6 Gm.		8:55 a.m.	108		3:25	143			0.6 Gm.	3:50	136
9:25	150		2:35	110		9:45	100		3:55	150		2:40	106	2/22/41	
9:30	Quinidine		3:00	104		9:55	107		4:25	141		3:00	106	10:45 a.m.	115
	0.6 Gm.		3:30	108		10:00	Quinidine		11/13/41			3:30	113		
10:45	150		4:00	108			0.6 Gm.		11:15 a.m.	120		4:00	118		
11:30	144		4:15	115		11:00	128					4:05	109		
			5:15	124		12:00	107					5:15	100		
						1:00 p.m.	136					2/ 8/41			
												12:05 p.m.	88		

and two hours later the electrocardiogram again showed transient right bundle branch block (Fig. 2). Multiple precordial leads again showed relatively late activation of the right ventricle at the time when the bundle branch block was present. This observation is of interest in connection with the interpretation of the aberrant ventricular deflections which are sometimes observed after the administration of quinidine to patients with auricular fibrillation.

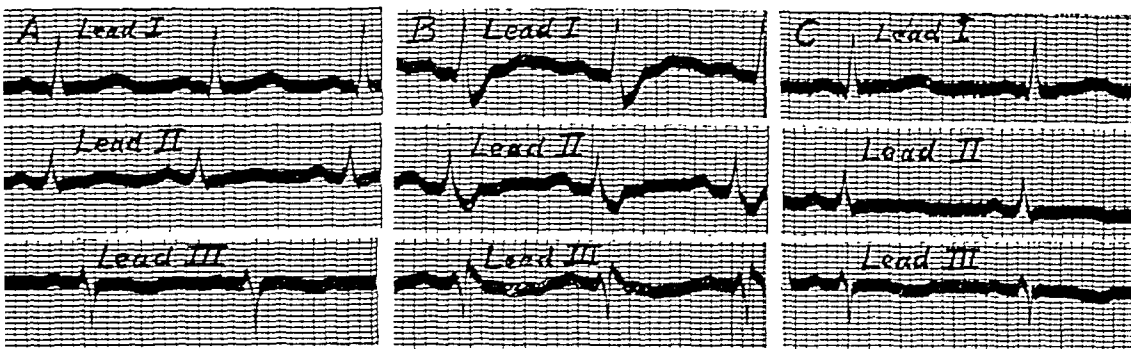


Fig. 1.—Quinidine sulfate, 0.6 Gm., by mouth at 2:00 P.M. A, Control curve, 1:55 P.M. B, Right bundle branch block, 4:05 P.M. C, The following day, 12:05 P.M.

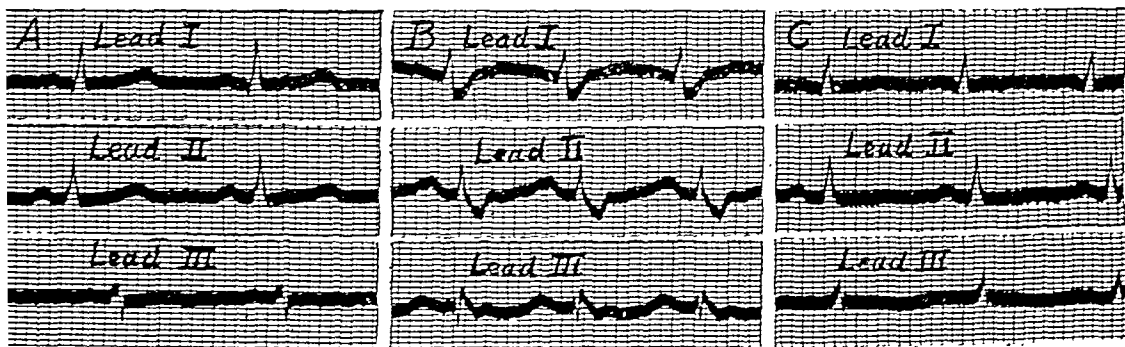


Fig. 2.—Two weeks after Fig. 1. Quinidine sulfate, 0.6 Gm., by mouth at 1:45 P.M. A, Control curve, 1:35 P.M. B, Right bundle branch block, 3:50 P.M. C, The following day, 10:45 A.M.

When quinidine is administered in the treatment of auricular fibrillation, and its effects followed closely by means of frequent electrocardiograms, approximately one-third of the patients show abnormal QRS deflections.^{2, 3} These resemble the abnormal complexes of ectopic ventricular beats or of defective intraventricular conduction. They occur at the height of the quinidine effect, and disappear shortly after the quinidine has been stopped.

It has been abundantly demonstrated that quinidine depresses intraventricular conduction, as shown by prolongation of the QRS interval,²⁻⁹ and the abnormal QRS complexes which follow quinidine have been attributed by some observers to defective intraventricular conduction.^{3, 5, 7, 9} Furthermore, it is well known that quinidine may abolish ectopic ventricular beats, and that it is especially effective in stopping

ventricular paroxysmal tachycardia.^{10, 11, 12} Nevertheless, the abnormal QRS deflections which follow quinidine have been attributed by some observers to ectopic ventricular beats.^{2, 6, 10, 13}

In auricular fibrillation, quinidine almost invariably causes an increase in ventricular rate. This makes it specially difficult to distinguish between abnormal deflections caused by ectopic premature ventricular beats, occurring singly or in runs, and those caused by defective intraventricular conduction, which would be especially likely to appear at higher rates or after the shorter diastoles. Lewis and his associates² have pointed out that there should be a close relation between prematurity and abnormality of ventricular deflections, if the abnormality were the result of impaired conductivity. They recognized that, in a general way, such a relationship existed, but did not consider it sufficiently close to indicate impaired intraventricular conductivity. In published electrocardiograms showing abnormal ventricular deflections which are attributed to ectopic ventricular beats caused by quinidine, alternative interpretations are possible, namely, that the ectopic beats occurred spontaneously or for some other reason, and were not caused by quinidine, or that the deflections were aberrant because of impaired intraventricular conductivity.^{6, 14}

White, Marvin, and Burwell⁵ mentioned a case in which quinidine produced marked intraventricular block without abolishing the auricular fibrillation. Korns⁷ published curves from a patient who showed bundle branch block after 6 grams of quinidine, which disappeared shortly after withdrawal of the drug: auricular fibrillation was present and the ventricular rate was 90 per minute, both in the presence of the bundle branch block and in its absence. Wilson, Wishart, Clark, and Herrmann³ described a case of auricular fibrillation in which all of the ventricular deflections became abnormal after 1.6 Gm. of quinidine. Normal rhythm returned two hours later, and all of the ventricular deflections were still abnormal; the normal type returned, however, as soon as the quinidine effect passed off. The abnormal deflections were attributed to impaired intraventricular conductivity.

In the present case, the aberrant ventricular deflections were clearly the result of impaired intraventricular conductivity caused by quinidine. It is our opinion that when quinidine causes abnormal QRS deflections, it does so by depressing conduction within the ventricles.

SUMMARY

A single dose of 0.6 Gm. of quinidine sulfate was given by mouth to each of five patients with sinus tachycardia. The cardiac rate was either not affected or was slightly increased.

In one patient, transient right bundle branch block occurred two hours after the administration of quinidine, upon two separate occasions.

When quinidine causes abnormal QRS deflections, it does so by depressing conduction within the ventricles.

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AURICULAR PAROXYSMAL TACHYCARDIA WITH AURICULOVENTRICULAR BLOCK

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AURICULAR paroxysmal tachycardia is a condition in which the heart beats rapidly and regularly in response to impulses arising in the auricles. The attacks are characterized by abrupt transitions, from normal rhythm to tachycardia at their onset, and from tachycardia to normal rhythm at their termination. They usually last a few minutes or a few hours, rarely much longer. The rate is usually between 150 and 220 per minute, commonly near 200. The ventricles respond, as a rule, to each auricular beat. The attacks can often be stopped by pressure upon the carotid sinus, or by large doses of digitalis, less commonly by quinidine. The precise mechanism of the auricular tachycardia is not understood. It is commonly believed that a rapid succession of impulses arises from an ectopic focus in the auricles. It is possible that in some manner each beat initiates the succeeding beat, or that the tachycardia depends upon the establishment of a circus rhythm in the auricular muscle. This last possibility has been discussed in considerable detail by Lewis.¹ It is of interest that auricular paroxysmal tachycardia seldom occurs in patients who have had previous attacks of auricular flutter or fibrillation, and that these disturbances, which are caused by circus rhythm, are uncommon in patients who have had auricular paroxysmal tachycardia.

In auricular flutter the auricular activity is characterized by a high degree of regularity and uniformity. The auricular rate is usually between 240 and 375 per minute. The ventricles very rarely respond to each auricular impulse; there is nearly always partial atrioventricular block, commonly 2:1. The abnormal mechanism is usually more persistent than auricular paroxysmal tachycardia, and often lasts for weeks or months, but repeated short attacks sometimes occur. Carotid sinus pressure slows the ventricles but does not alter the auricular mechanism. Digitalis slows the ventricles, and, when large amounts are given, usually converts auricular flutter into auricular fibrillation. Quinidine always slows the auricular rate, but does not often restore normal rhythm.

In rare instances of auricular paroxysmal tachycardia, the ventricles do not respond to each auricular beat in the usual manner. There may

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TABLE
AURICULAR PAROXYSMAL TACHYCARDIA

	AUTHORS	AGE	SEX	DURATION OF SYMPTOMS	FREQUENCY OF ATTACKS	DURATION OF ATTACKS	AUR. RATE	DEGREE OF A-V BLOCK	P WAVES*		
									LI	LII	LIII
1.	Koplik, 1917	10	M	2 years			200	2:1 to 3:1			
2.	Singer and Winterberg, 1922	70	M				184	complete		+	
3.	Gallavardin, 1923	60	F	a few hours	one attack	a few hours	180	2:1		+	
4.	Lenhartz and Samet, 1924	29	F	3 years	3 attacks	up to 94 days	196 to 188	2:1	-	+	+
5.	Sprague and White, 1925	48	F	10 years	4 days to 7 months	several hours	190 to 270	2:1	+	-	-
6.		23	F	6 months	20 attacks	2 hours to 5 days	220	2:1	+	+	+
7.		26	M	10 years	daily to 7 months	a few minutes	166 to 190	2:1		+	
8.						several hours	180	3:1 to 6:1			-
9.	Wenckebach & Winterberg, 1927	20	M	7 weeks	numerous	variable	180	3:2 to 2:1		+	
10.				many years		4 weeks	205	dropped beats	(+, lead not stated)		
11.	Dock, 1928	38	F	22 days	one attack	22 days	186 to 180	2:1 to 4:1	?	+	+
12.	Mackinnon, 1934	17	M	at least 5 days	one attack	at least 5 days	121	2:1	(+, lead not stated)		
13.		45	F	2 years	daily	a few minutes	150	dropped beats	(?, lead not stated)		
14.	Brown, 1936	40	F	8 years		a few minutes, persistent	214	2:1	-	+	+
15.	Maddox, 1937	39	F	17 years	2 to 5 years	up to 69 days	120 to 170	1:1 to 3:1	+	-	-
16.	Maarssø, 1937	8	M	1 year		1 month	182 to 160	dropped beats, 2:1	?	?	+
17.	Fine and Miller, 1940	16	F	several years	daily	brief	120 to 200	dropped beats	-	+	+
18.	Case 1	39	M	9 years	upon exertion	brief	170, 150	1:1 to 3:1		+	
19.	2	32	M	10 years	daily to several weeks	up to 26 days	200	1:1 to 2:1	+	+	-

*During paroxysmal tachycardia. +, upright; -, inverted; ±, diphasic, upward and then downward; †, diphasic, downward and then upward; ?, not visible.

I
 WITH AURICULOVENTRICULAR BLOCK

INTENSITY	CONGESTIVE FAILURE	ORGANIC HEART DISEASE	INEFFECTIVE TREATMENT	EFFECTIVE TREATMENT	RESULT	REMARKS
moderate	none	none				electrocardiograms not published
				quinine	stopped the paroxysm	
		syphilitic aortitis			normal rhythm	
marked	none	none	quinine	digitalis and physostigmine	normal rhythm	aur. rate slowed by quinine and by digitalis and physostigmine
moderate	none	none	quinidine	digitalis, removal of cervical ribs	normal rhythm	
moderate	none	none	quinidine	digitalis, rest	normal rhythm	
slight	none	none	quinidine	digitalis	normal rhythm	
				quinine	normal rhythm	
		none			normal rhythm	
				quinine	normal rhythm	
marked	present	mitral stenosis	digitalis		A-V bradycardia	
marked	present	mitral stenosis, aortic regurg.		digitalis	increased block, normal rhythm	
slight	none	mitral lesion		carotid sinus pressure	normal rhythm	probable case, P not identified
marked	acute edema of lungs	mitral and pulmonary lesions or congenital heart		digitalis	normal rhythm	changed to aur. fibr. and then to normal rhythm after digitalis
moderate	none	none	quinine quinidine digitalis neostyletholine	rest	normal rhythm	sinus tachycardia influenced by rest, exercise, emotion, sleep; auricular rate slowed by digitalis
present	none	enlargement	digitalis			
moderate	none	none	carotid sinus pressure	digitalis, quinidine	normal rhythm	rate influenced by posture
slight	none	none	quinidine	digitalis	increased degree of block	normal rhythm later
marked	none	mitral stenosis	quinidine quinine mecholy	digitalis, rest	increased degree of block, improved	also auricular flutter and fibrillation

TABLE

	AUTHORS	AGE	SEX	DURATION OF SYMPTOMS	FREQUENCY OF ATTACKS	DURATION OF ATTACKS	AUR. RATE	DEGREE OF A-V BLOCK	P WAVES*		
									LI	LII	LIII
20.	3	41	M	1 year	a few days to 6 months	a few minutes	174 to 218	1:1 to 3:1	+	+	+
21.	4	15	M	3 months	almost continuous	up to 60 days	167 to 129	1:1 to 3:2	?	±	+
22.	5	62	F	10 months		1 day	167, 158	dropped beats	+	+	+
23.	6	19	M	6 months	upon exertion	at least 13 days	136 to 160	1:1 to 3:1	+	-	-
24.	7	67	M		4 to 14 days	up to 2 days	188 to 235	1:1 to 3:1	?	+	+
25.	8	53	M	2 days	one attack	2 days	188	usually 2:1	?	+	+
26.	9	23	F	6 months	up to 7 days	1 hour to 2 days	195	1:1 to 2:1	+	+	+
27.	10	54	M	4 days	one attack	4 days	200	2:1 or greater	+	+	+
28.	11	52	M	3 days	one attack	3 days	161 to 167	dropped beats	+	+	+
29.	12	80	M	3 days	one attack	3 days	215	usually 4:1	+	+	+
30.	13	68	M	2 days	one attack	2 days	137	2:1	+	+	+
31.	14	17	F	2 days	one attack	2 days	130	dropped beats	+	+	+
32.	15	64	M	9 months	several times daily	a few minutes	192 to 250	2:1 briefly	+	-	-
33.	16	26	F	9 months	9 months		160	complete	+	+	+
34.	17	48	M	3 days	one attack	3 days	180 to 163	2:1	± +	+	+
35.	18	45	M	10 days	2 attacks	1 hour and 2 days	212	2:1 to 3:1	+	+	+

*See footnote, p. 766.

be occasional dropped ventricular beats, or 2:1 or higher grades of auriculoventricular block. Auricular paroxysmal tachycardia associated with heartblock differs in several important respects from ordinary paroxysmal tachycardia of auricular origin, and resembles auricular flutter in some particulars. The purpose of this paper is to review seventeen previously reported cases, to present eighteen additional cases, and to describe some of their peculiarities. The important features of these thirty-five cases have been tabulated (Table I).

I—CONT'D

DIS-ABILITY	CONGES-TIVE FAILURE	ORGANIC HEART DISEASE	INEFFEC-TIVE TREATMENT	EFFECTIVE TREATMENT	RESULT	REMARKS
moderate to marked	none	none	quinidine mechoyl	digitalis	increased degree of block	normal rhythm later, aur. rate slowed by quinidine
marked	present	none	quinidine digitalis	none	died 84 days after onset	aur. rate slowed by quinidine. Autopsy
slight	none	none		digitalis	normal rhythm	
moderate to marked	none	? mitral lesion	digitalis mechoyl	quinidine	normal rhythm; died suddenly	aur. rate slowed by quinidine. Autopsy
moderate	none	hypertension, arteriosclerosis, emphysema	digitalis	quinidine	normal rhythm	
inci-dental	present	right-sided enlargement	digitalis		died	autopsy; bronchiectasis
moderate	none	mitral stenosis, aortic regurg.	digitalis	quinidine	normal rhythm	
slight	none	hypertension, slight enlargement	digitalis (overdigitalized)	stopped digitalis	normal rhythm	changed to aur. fibr. and then to normal rhythm
marked	present	hypertension, enlargement		digitalis	normal rhythm	developed acute edema of lungs
inci-dental	none	arteriosclerosis	digitalis			changed to auricular fibrillation
none	none	arteriosclerosis			normal rhythm	
none	none	exophthalmic goitre			normal rhythm	
slight	none	arteriosclerosis, slight enlargement	quinidine	digitalis	normal rhythm	A-V block very brief
marked	present	hypertension, enlargement		digitalis	normal rhythm	
inci-dental	acute edema of lungs	acute myocardial infarction, hypertension, enlargement	digitalis		normal rhythm	P waves vary in form
inci-dental	present	old myocardial infarction	digitalis		normal rhythm	

PREVIOUSLY REPORTED CASES

The first report of auricular paroxysmal tachycardia with partial A-V block was by Koplik,² in 1917. The patient was a 10-year-old boy. Many electrocardiograms were obtained, but none were published. In 1922, Singer and Winterberg³ published curves from a 70-year-old man whose A-V block was complete, with a ventricular rate of 26 per minute. The auricular paroxysmal tachycardia was stopped by quinine given intravenously. Gallavardin,⁴ in 1923, described a case in which there were frequent dropped ventricular beats and short periods of 2:1 A-V

block interspersed with short runs of 1:1 response. He pointed out that such a disturbance could give rise to almost complete irregularity of the ventricles at a rapid rate, closely resembling auricular fibrillation clinically. In 1924, Lenhartz and Samet⁵ reported a case in a 29-year-old nurse who for a long time was thought to have auricular fibrillation. Normal rhythm was finally restored by the combined use of physostigmine and digitalis after the attack had lasted ninety-four days. Sprague and White,⁶ in 1925, reported three cases, and briefly compared and contrasted them with auricular flutter. They pointed out that the attacks occurred over a period of years, often lasted several days, and were not influenced favorably by quinidine, but could often be stopped by digitalis in full doses. In 1927, Wenckebach and Winterberg⁷ reported three cases, in two of which normal rhythm was restored by quinine. Dock,⁸ in 1928, described a case in which the auricular paroxysmal tachycardia lasted for twenty-two days and was accompanied by partial A-V block varying in degree from 2:1 to 4:1, and was not affected appreciably by pressure upon the carotid sinus or the eyes or by large amounts of digitalis. In 1934, Mackinnon⁹ reported two cases. One of these was clearly an instance of auricular paroxysmal tachycardia with partial A-V block. The other was similar in most important respects, but can be considered only as a probable case because the auricular waves could not be identified in the records. The author pointed out that in occasional cases of auricular paroxysmal tachycardia the ventricular rhythm may be irregular, and that the usual cause for this irregularity is defective conduction in the A-V bundle.

Brown,¹⁰ in 1936, presented esophageal leads of two patients, which he interpreted as showing auricular paroxysmal tachycardia with partial A-V block. The first of these curves is susceptible of an alternative interpretation, namely, that, while the rate was rapid, the ventricular complexes were slightly aberrant and thus gave the curve an appearance which somewhat resembled auricular paroxysmal tachycardia with partial A-V block. The second case, however, is clearly a very interesting example of the condition under discussion, and illustrates the value of digitalis in its treatment. The author called attention to the differences between auricular paroxysmal tachycardia and auricular flutter as shown by esophageal leads. In the former the auricular deflections are separated one from another by intervals during which the tracing remains at the isoelectric level. In flutter, however, the auricular activity produces a continuous oscillation of the tracing, with no isoelectric intervals, suggesting continuous excitation.

In 1937, Maddox¹¹ reported a case of auricular paroxysmal tachycardia with variable A-V conduction and periods of 2:1 or 3:1 block. His discussion deals mainly with the site of impulse formation and the influence of the extrinsic cardiac nerves. Maarssø,¹² in 1937, reported a case in which an attack of auricular paroxysmal tachycardia lasted longer than one month. At times there was partial A-V block, varying

in degree from frequent dropped beats to 2:1 response. Fine and Miller,¹³ in 1940, reported a remarkable case of orthostatic auricular paroxysmal tachycardia in which the rate was influenced by posture. Sometimes the paroxysmal tachycardia was present while the patient was recumbent, and was then sometimes accompanied by partial A-V block with frequent dropped beats. The attacks of paroxysmal tachycardia could be prevented by either digitalis or quinidine.

Lewis¹ published electrocardiograms of a child with auricular paroxysmal tachycardia and partial A-V block with occasional dropped beats. The auricular rate was 290 per minute, and the P waves were upright in Lead II. Recently, Katz¹⁴ has published the curves of three patients who had partial A-V block during paroxysms of auricular tachycardia. The first of these showed auricular rates of 180 to 125 and block varying in degree from dropped beats to 2:1. The second had an auricular rate of 158 and 2:1 block. The third patient had an auricular rate of 167 and frequent dropped beats. In all three cases the P waves were upright during the paroxysms. These cases are not included in the table because the clinical data were not given.

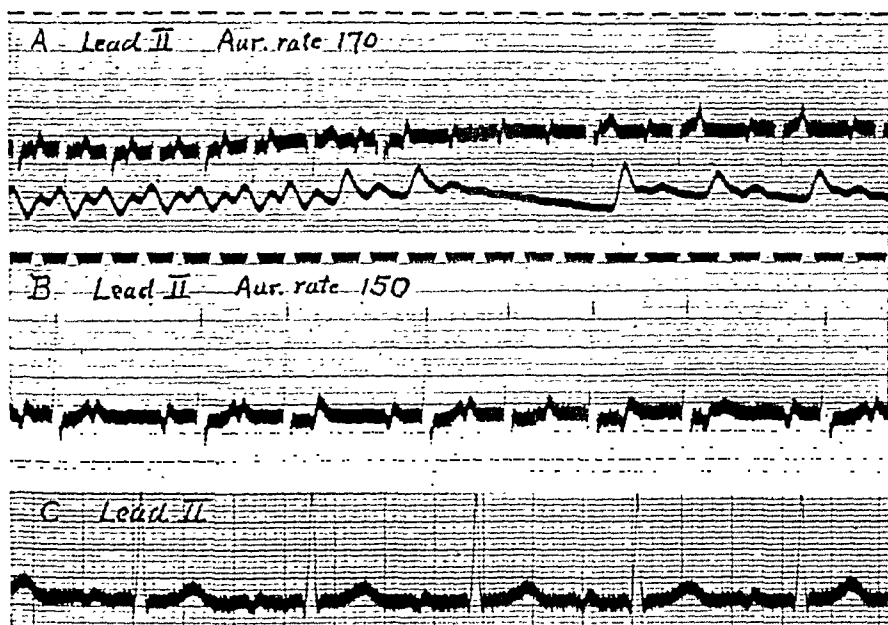


Fig. 1.—Case 1. A, March 22, 1922. Lead II and radial pulse. Auricular rate, 170. B, Aug. 2, 1922. Lead II. Auricular rate 150. C, July 26, 1924. Lead II. Normal rhythm, rate 90.

CASE REPORTS

CASE 1.*—A white man, aged 39 years, was first seen in 1922. He complained of attacks of palpitation and dyspnea brought on by exertion. These began in 1913, and had been worse since 1917. Examination revealed no evidence of organic heart disease and no signs of congestive cardiac failure. The electrocardiogram (Fig. 1, A and B) showed diphasic P waves, occurring at a rate of 170 per minute.

*This case is included through the kindness of Dr. John Parkinson, London, England, who generously furnished the electrocardiograms and the clinical data.

Partial A-V block of varying degree (1:1, 3:2, 2:1) was present. Full doses of quinidine sulfate had no effect on the auricular deflections. The average ventricular rate was somewhat increased and the ventricular complexes became aberrant. One week later digitalis was given in full doses. This increased the degree of A-V block (frequently 3:1), but had no further effect. In 1924, an electrocardiogram showed normal rhythm with diphasic P waves and a rate of 90 (Fig. 1, C). In 1927, the patient stated that he had been fairly well, and tracings again showed normal rhythm with diphasic P waves and a rate of 100.

CASE 2.—A white man, 32 years of age, was first seen Oct. 28, 1937. At the age of 12 years he had rheumatic fever. He had a brief attack of tachycardia in 1928, and another in 1929. After that he had frequent attacks of tachycardia, brought on by slight exertion, by eating large meals, or by constipation, and sometimes relieved by rest. The paroxysms sometimes lasted for several hours or days, and were then accompanied by shortness of breath and soreness in the region of the liver. They became so frequent, so prolonged, so severe, and so resistant to treatment that recourse was had to morphine, with resulting addiction.

When first seen, the patient was exhausted from a prolonged attack of tachycardia. The heart rate was 200, the rhythm regular. Pressure upon the carotid sinus caused no change. Mecholyl, in a dose of 25 mg., was given subcutaneously, and repeated fifteen minutes later. After this the heart rate became a little slower, and upon carotid sinus pressure it fell to a normal level. Almost immediately, however, the rapid beating returned.

At this point the first electrocardiogram was taken; it showed auricular flutter with an auricular rate of 286, and 2:1 ventricular response. Digitalis, in a dose of 0.5 Gm., was given intravenously, and thirty minutes later the electrocardiogram (Fig. 2, A) showed auricular flutter with an auricular rate of 275 and a ventricular rate of 82 per minute. On October 29, digitalis, in a dose of 0.35 Gm., was given intravenously. On November 1 the electrocardiogram (Fig. 2, B) showed auricular paroxysmal tachycardia with auricular and ventricular rates of 200. Digitalis (0.35 Gm.) was given intravenously, and fifteen minutes later there was 2:1 A-V block; the auricular rate was still 200 (Fig. 2, C). After this, digitalis was given orally in rather large amounts. The auricular paroxysmal tachycardia continued, but partial A-V block was maintained, and on November 22 the electrocardiogram (Fig. 2, D) showed an auricular rate of 200 and a ventricular rate of 64, sometimes even lower. Precordial leads were used in order to obtain large auricular deflections. At this time digitalis was stopped because of symptoms of mild intoxication. On November 26 there was 1:1 ventricular response with a rate of 200. Carotid sinus pressure caused partial block. After giving mecholyl (25 mg. subcutaneously), carotid sinus pressure caused pronounced slowing of the ventricles. Esophageal leads were used to record this (Fig. 2, E), and showed large auricular deflections separated by periods of electrical quiescence. Digitalis was resumed. On Dec. 29, 1937, normal rhythm was present (Fig. 2, F). For several months after this there were many attacks of tachycardia. The patient then improved and it was thought that normal rhythm was present much of the time. At this time the murmur of mitral stenosis was heard. On Oct. 28, 1938, however, an electrocardiogram showed auricular flutter in Leads I and II, with an auricular rate of 292 and a 4:1 ventricular response. A minute later, when Lead III was taken, auricular fibrillation was present, with a ventricular rate of 80. In order to bring out the auricular waves more clearly, a precordial lead was used (Fig. 2, G).

CASE 3.—A white man, aged 41 years, was first seen on Jan. 5, 1938. For one month he had been having attacks of tachycardia, shortness of breath, and dizziness. They occurred irregularly every few days and lasted a few minutes. They were abrupt in onset and termination, and were brought on by exertion and relieved by

rest. Similar attacks had occurred one year previously and again six months previously, each time for a period of a few weeks.

Physical examination was entirely negative. No abnormality of the heart was detected. The blood pressure was 118/60. The rhythm was regular, the rate, 100. With moderate exercise, however, the rate rose to more than 160; the rhythm was regular. After about thirty seconds the rate dropped abruptly and the rhythm was

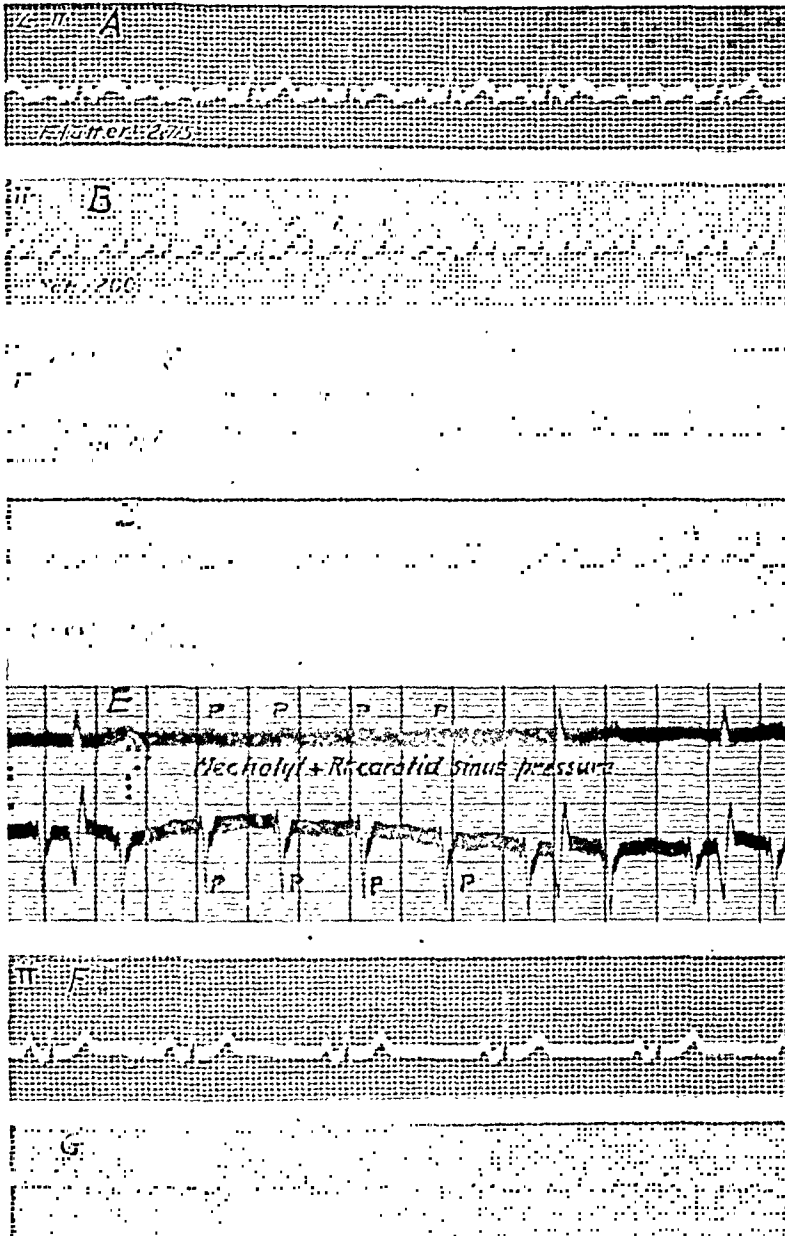


Fig. 2.—Case 2. *A*, Oct. 28, 1937. Lead II. Auricular flutter. Auricular rate 275, ventricular rate, 82. *B*, Nov. 1, 1937. Lead II. Auricular paroxysmal tachycardia with auricular and ventricular rates of 200. Patient had had digitalis (0.85 Gr.). *C*, Nov. 1, 1937. Lead II, 15 minutes after 0.35 Gm. of digitalis intravenously. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 200. *D*, Nov. 22, 1937. Precordial lead. Auricular paroxysmal tachycardia with high grade partial A-V block. Auricular rate 200. Patient had had large amounts of digitalis. *E*, Nov. 26, 1937. Lead I and esophageal lead. Pressure upon right carotid sinus after 25 mg. of mechohyl subcutaneously. *F*, Dec. 29, 1937. Lead II. Normal rhythm. *G*, Oct. 1, 1938. Precordial lead. Auricular fibrillation.

irregular for 10 or 15 beats. Thereafter the heart beat regularly at a normal rate. The exercise was repeated and the same changes in rate and rhythm were again observed.

An electrocardiogram (Fig. 3, *A*) showed paroxysmal tachycardia with an auricular rate of 200 and partial A-V block, usually 3:1. A precordial lead (Fig. 3, *B*) was employed to show the auricular waves more clearly. Exercise permitted the ventricles to follow the auricles at their full rate for a short time, after which the partial block returned. Carotid sinus pressure and mecholyl failed to terminate the auricular tachycardia. Quinidine sulphate, in a dose of 0.4 Gm. orally, was followed in two hours by slowing of the auricles to 174; the ventricles followed at

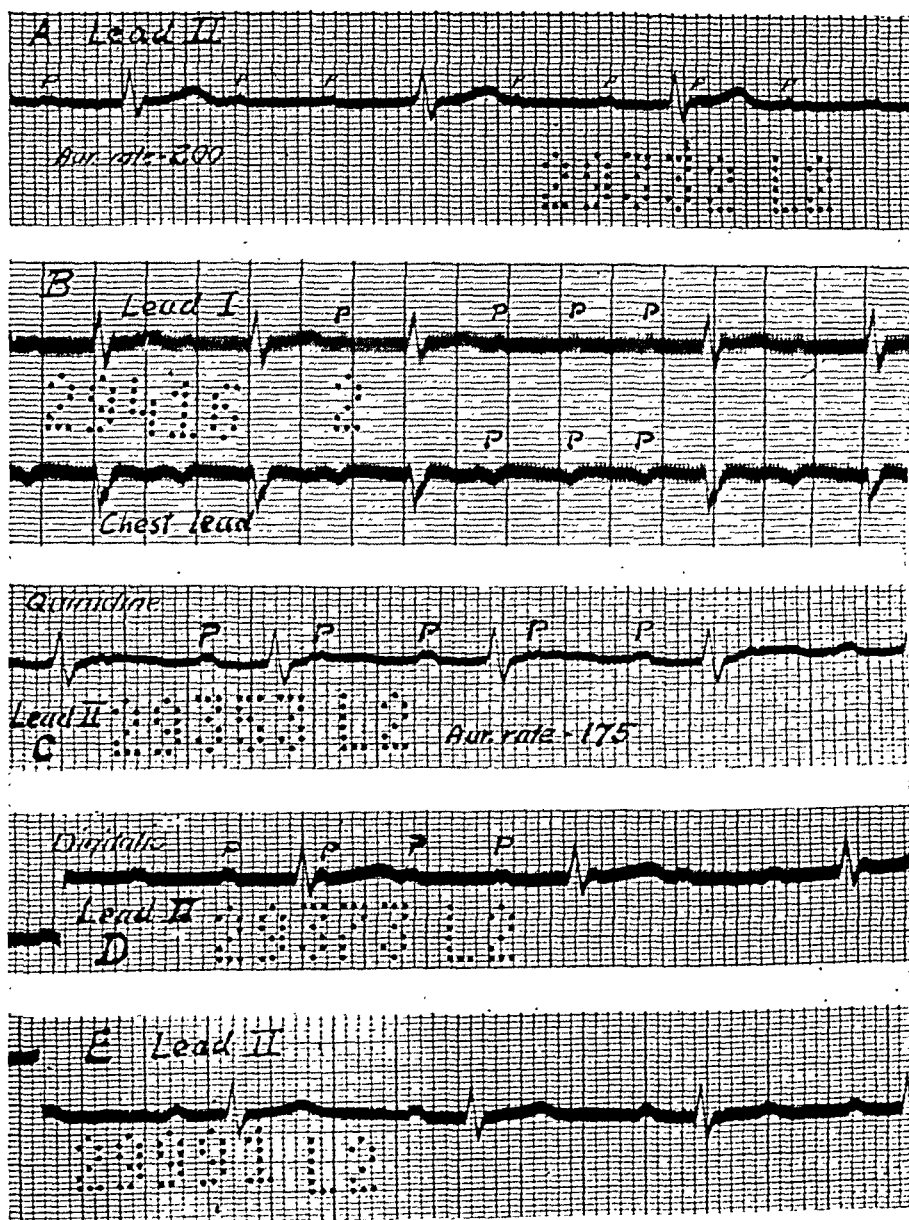


Fig. 3.—Case 3. *A*, Jan. 5, 1938. Lead II. Auricular paroxysmal tachycardia with partial A-V block. Auricular rate 200. Ventricular 78. *B*, Jan. 5, 1938. Lead I above and precordial lead below. Pressure upon right carotid sinus. Auricular rate 200. *C*, Jan. 7, 1938. Lead II, 2 hours after 0.4 Gm. of quinidine sulfate. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate, 175. Ventricular rate, 87. *D*, Jan. 10, 1938. Lead II, after 1.3 Gm. of digitalis. Auricular paroxysmal tachycardia with 3:1 A-V block. Auricular rate, 202. Ventricular rate, 67. *E*, March 17, 1938. Lead II. Normal rhythm, rate 88. Had taken digitalis regularly.

half the auricular rate (Fig. 3, C). Normal rhythm, however, was not restored. The patient was then digitalized without affecting the auricular rate. The degree of block, however, was increased, usually to 3:1 (Fig. 3, D), and the rapid ventricular beating upon exertion was prevented. After digitalization it was observed that mecholyl, in a dose of 15 mg. subcutaneously, increased the auricular rate from 207 to 218; the ventricular rate rose to 109.

Digitalis was continued. The patient returned January 26, at which time he had complete relief from his symptoms. The auricular rate was 211, and the ventricular rate, 86, with a mixture of 2:1 and 3:1 block. On March 17 the patient stated that he had been entirely free of symptoms, and the electrocardiogram showed normal rhythm (Fig. 3, E).

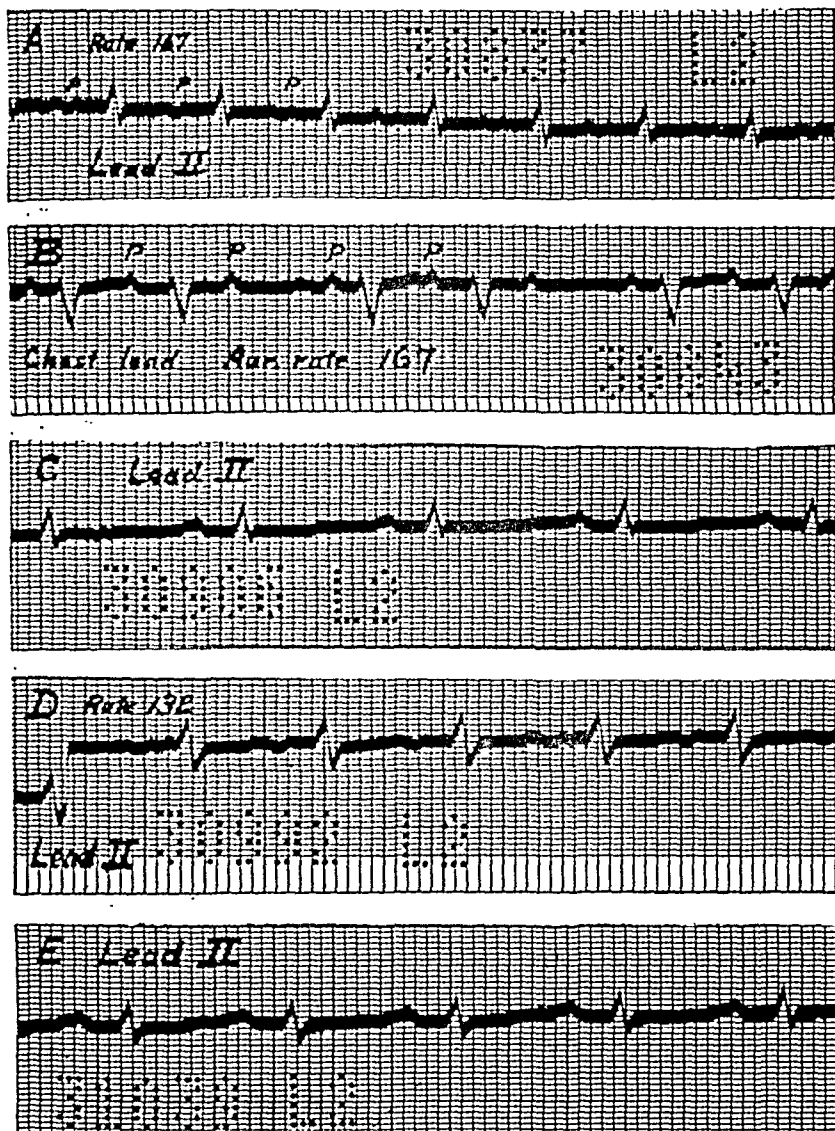


FIG. 4.—Case 4. A, June 21, 1938. Lead II. Auricular paroxysmal tachycardia, rate 167. Patient had received quinidine and digitalis. B, June 21, 1938. Precordial lead, with carotid sinus pressure. There is partial A-V block with dropped beats. The auricular deflections are shown more clearly. Auricular rate 167. C, June 29, 1938. Lead II. Normal rhythm. Rate 97. Had had digitalis and quinidine. D, July 11, 1938. Lead II. Auricular paroxysmal tachycardia with 1:1 ventricular response. Rate 132. Had had digitalis and quinidine. E, July 18, 1938. Lead II. Normal rhythm. Rate 107.

CASE 4.—A white boy, 15 years of age, was admitted to the hospital June 21, 1938. He had been in excellent health until May 1, 1938 when he began having shortness of breath upon moderate exertion, tachycardia, weakness, and an unproductive cough. The patient was not aware of an abrupt onset, nor was there any known infection at the time. The tachycardia persisted around 200 per minute in spite of rest in bed. The shortness of breath was increased by lying flat. Digitalis slowed the ventricles by producing partial A-V block. Quinidine slowed the auricular rate but was otherwise without appreciable effect. The patient grew weaker and more dyspneic, and the liver became enlarged. He was then referred to the hospital.

Upon physical examination the patient appeared seriously ill, with a dusky cyanosis, and dyspnea upon lying flat. The heart was moderately enlarged. There was a systolic murmur over the entire heart, loudest at the apex. No diastolic murmur was heard. The rate was about 160; the rhythm was not remarkable apart from an occasional, slight irregularity. The blood pressure was 92/70. The lungs were normal. The liver was slightly enlarged. There was no edema.

Röntgenologic examination showed fairly marked cardiac enlargement.

The electrocardiogram showed a heart rate of 167; the rhythm was regular except for occasional dropped beats (Fig. 4, *A*). Precordial leads showed the auricular deflections more clearly. Pressure upon the carotid sinus increased the degree of A-V block, causing frequent dropped beats (Fig. 4, *B*). Quinidine was withheld, and the auricular rate rose to 176; then quinidine was resumed and the auricular rate fell to 150. After the administration of both digitalis and quinidine for several days, normal rhythm returned (Fig. 4, *C*). In a few days, however, the tachycardia returned and persisted, except for a brief period of normal rhythm on July 18 (Fig. 4, *E*). During the ectopic auricular tachycardia, the rate slowed to 132 under digitalis and quinidine (Fig. 4, *D*). The patient grew progressively worse; he showed no improvement during the interludes of normal rhythm or when the rate slowed to 132. Râles appeared in the lungs and edema of the legs developed. The patient died July 24, 1938, of cardiac failure.

At autopsy the heart weighed 350 grams. It showed myocardial hypertrophy microscopically. There were marked subendocardial vacuolar degeneration and moderate subepicardial fatty infiltration. Infarction of the left ventricle in the region of the conduction apparatus was found. There was also a degenerative subendocardial lesion in the left ventricle, with necrosis, lymphocytic infiltration, and fibroblastic proliferation. An organizing mural thrombus was present in the left ventricle. There was endocardial sclerosis.

The lungs showed an acute exacerbation of chronic passive congestion, with edema. There were multiple fresh, and older, hemorrhagic infarctions. There were organizing thrombi in the pulmonary veins. The smaller arteries were sclerotic. There was an embolus in a medium-sized pulmonary artery, and a bland embolus in the main pulmonary artery. Acute purulent bronchitis and terminal purulent lobular pneumonia were present.

The liver and spleen showed chronic passive congestion.

CASE 5.—A white woman, aged 62 years, entered the hospital July 11, 1938. During the previous ten months she had had recurring attacks of left-sided renal colic, suffered from increasing weakness, and had lost 35 pounds in weight. During this time she was short of breath upon moderate exertion, and experienced frequent palpitation and irregularity of the heart. There was occasional swelling of the ankles.

Physical examination showed that the heart was normal in size. There was a systolic murmur at the apex. The rate varied from 106 to 140. There was an irregularity which was attributed to dropped beats. The blood pressure was 130/85. The radial and brachial arteries were thickened. The lungs were normal. The

abdomen was negative. There was no edema. The isthmus of the thyroid contained a small adenoma.

Roentgenologic examination showed no abnormalities of the heart or lungs, but did reveal a renal calculus on the left side.

The electrocardiogram showed an auricular rate of 167. Partial A-V block, with frequent dropped beats, was present, and the ventricular rate was 134 (Fig. 5, *A*). Carotid sinus pressure increased the degree of block and slowed the ventricles, but did not alter the auricular mechanism (Fig. 5, *B*). After digitalis in full doses, normal rhythm returned (Fig. 5, *C*). The patient was sent back to her home physician for nephrectomy.

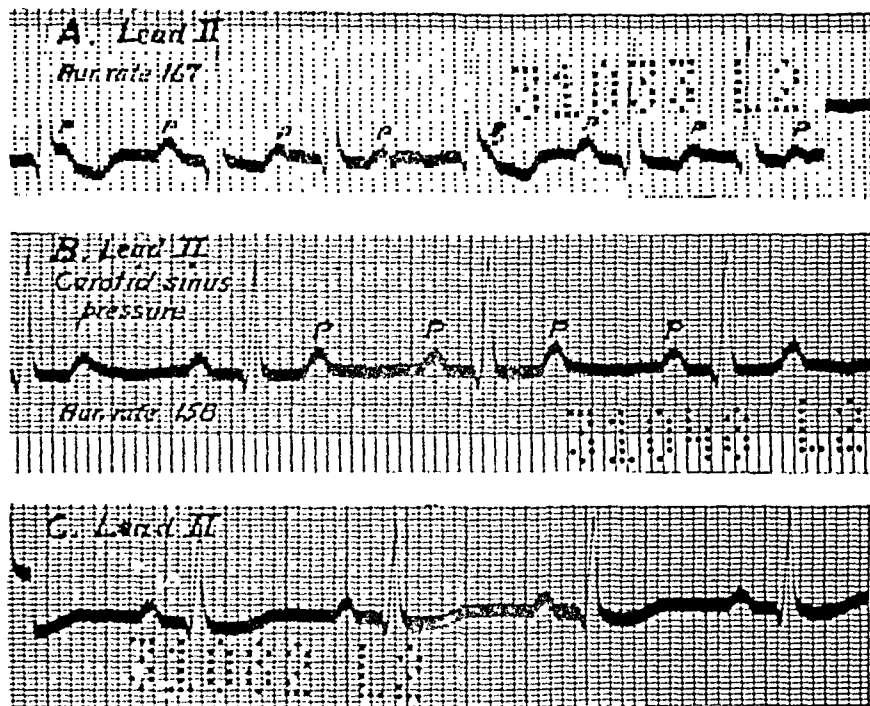


Fig. 5.—Case 5. *A*, July 18, 1938. Lead II. Auricular paroxysmal tachycardia with partial A-V block and frequent dropped ventricular beats. Auricular rate 167. *B*, July 19, 1938. Lead II. Carotid sinus pressure produces 2:1 A-V block. Auricular rate 150. *C*, July 22, 1938. Lead II. Normal rhythm. Rate 93. Had had digitalis.

CASE 6.—A white man, 19 years of age, was admitted to the hospital July 18, 1938. In 1930, the patient had had epigastric pain, nausea, and vomiting; these were attributed by his physician to heart disease, and were relieved in a few days by rest and digitalis. After that he took digitalis almost continuously and restricted his activities. Similar symptoms returned in 1933, and again in January, 1938. In each instance they followed strenuous exertion and were relieved by rest in bed. In January, 1938, he had a brief, acute respiratory infection. After that he had dyspnea and pronounced tachycardia upon moderate exertion. The heart was slow during rest. He improved under larger doses of digitalis and a month of rest in bed. The tachycardia upon exertion persisted, however, and he was referred to the hospital. There was no history of rheumatic fever.

The physical examination was entirely negative with the exception of the heart. It was markedly enlarged, with dullness extending to the left anterior axillary line. There were systolic murmurs at the apex and base. The rate and rhythm varied. At times the heart was regular at a rate of 60, at other times regular at a rate

of 170. Occasionally the rhythm was irregular and the rate intermediate between the two extremes. The blood pressure varied within normal limits. There were no signs of congestive cardiac failure.

Roentgenologic examination showed marked cardiac enlargement.

The electrocardiograms showed tachycardia of auricular origin, with a rate of 162 and 2:1 A-V block (Fig. 6, A). After mild exercise there was transient 1:1 ventricular response with no change in auricular rate. Carotid sinus pressure in-

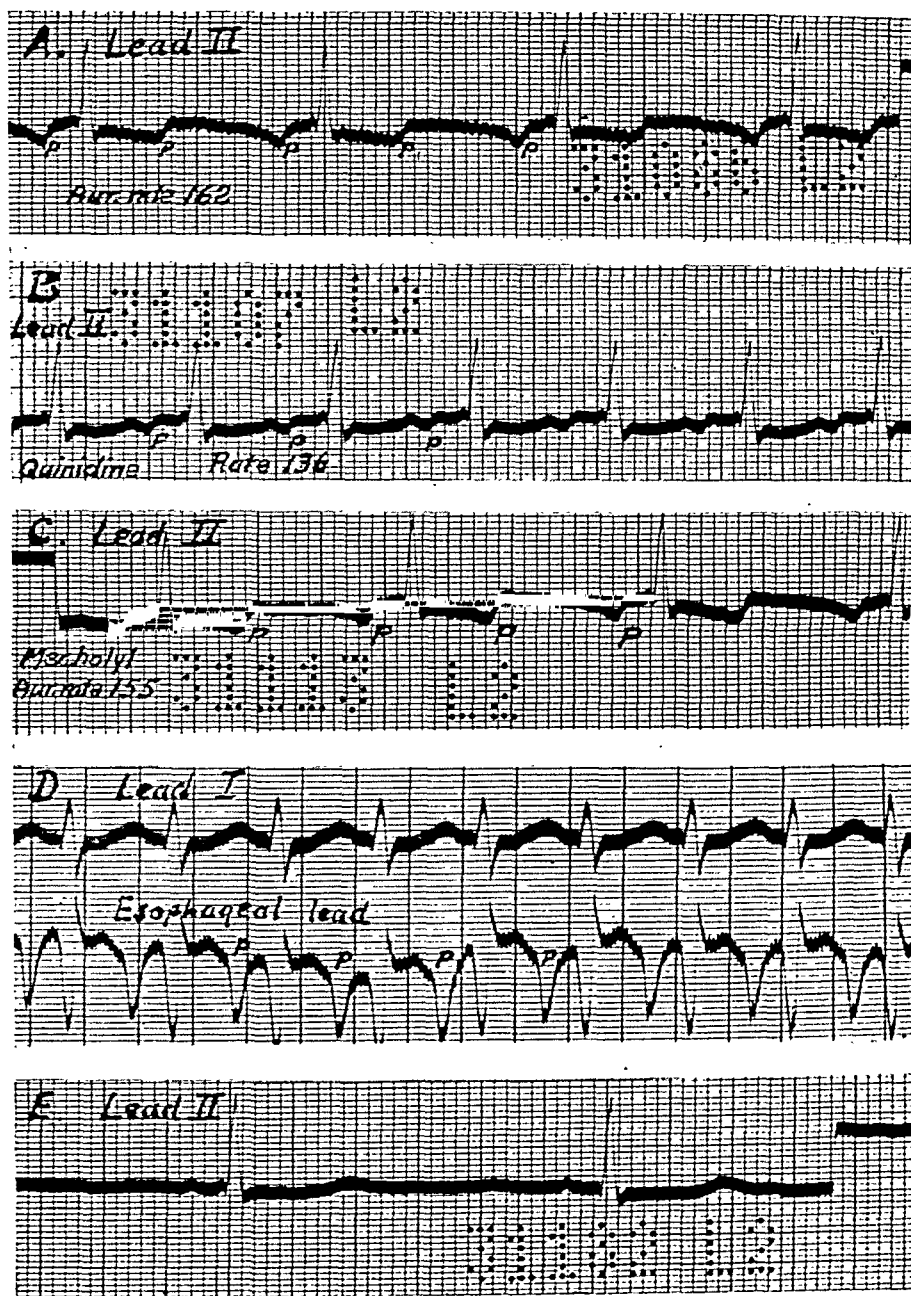


Fig. 6.—Case 6. A, July 22, 1938. Lead II. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 162. Had had digitalis. B, July 25, 1938. Lead II. Auricular paroxysmal tachycardia with 1:1 ventricular response. Rate 136. Had had digitalis and quinidine. C, July 26, 1938. Lead II, taken 33 minutes after 10 mg. of mecholyl subcutaneously. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 155. D, Aug. 8, 1938. Lead I above, esophageal lead below. Auricular paroxysmal tachycardia with 1:1 ventricular response. Rate 155. The auricular waves are very large in the esophageal lead. E, Aug. 3, 1938. Lead II. Normal rhythm. Rate 50. Had had digitalis and quinidine. Intraventricular block is present, but not readily apparent in this lead.

creased the degree of block temporarily, but did not affect the auricular mechanism or rate. Quinidine slowed the auricles to 136, usually with 2:1 ventricular response, but sometimes with 1:1 response (Fig. 6, *B*). Mecholyl, in a dose of 10 mg. subcutaneously, increased the degree of block slightly, but did not alter the auricular rate (Fig. 6, *C*). Normal rhythm returned on July 31, after large doses of quinidine sulfate (Fig. 6, *E*). On August 7 auricular paroxysmal tachycardia returned (Fig. 6, *D*). Normal rhythm was resumed after 0.9 Gm. of quinidine on August 8, and persisted thereafter. The patient was given quinidine sulfate in a dose of 0.3 Gm. three times daily. He felt quite well and there was no evidence of quinidine intoxication. He died unexpectedly in his sleep on Aug. 13, 1938.

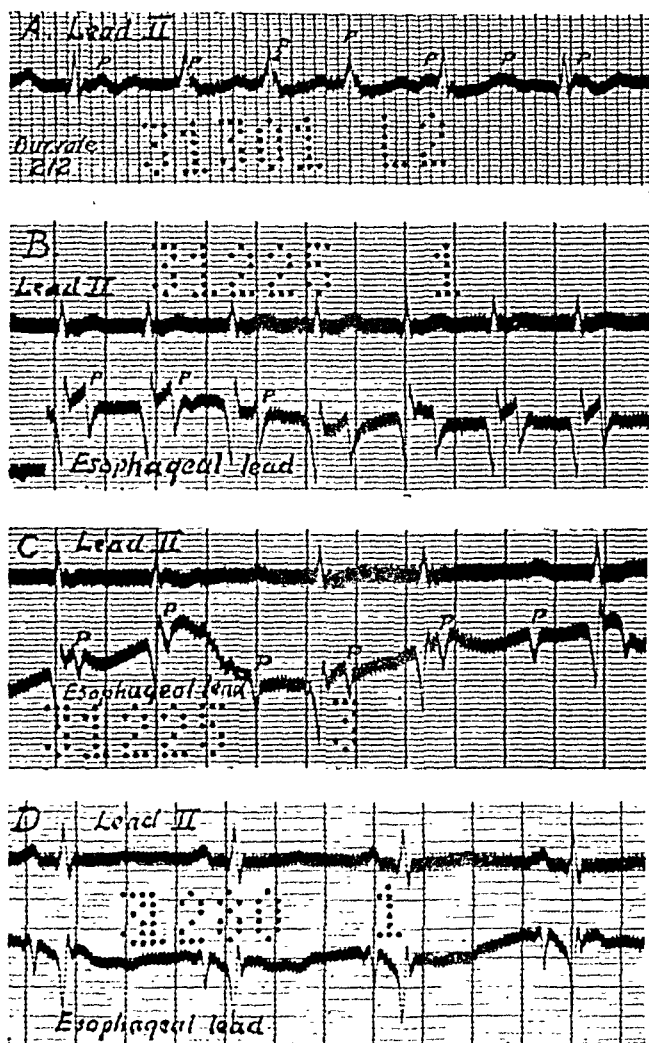


Fig. 7.—Case 7. *A*, Aug. 17, 1938. Lead II. Auricular paroxysmal tachycardia with partial A-V block and many dropped ventricular beats. Auricular rate, 212. Had had digitalis and quinidine. *B*, Aug. 6, 1938. Lead II above, esophageal lead below. There is 1:1 ventricular response. *C*, Same as *B*, but showing partial A-V block. *D*, Aug. 13, 1938. Lead II above, esophageal lead below. Normal rhythm. The auricular deflections are very large in the esophageal leads.

Autopsy showed hypertrophy of the left ventricle, the lateral wall of which measured 28 mm. in thickness. There was an old mitral valvulitis, with minimal deformity of the valve. The right side of the heart was dilated. The lungs showed congestion and edema, patchy emphysema, and atelectasis. There were acute puru-

lent bronchitis and microscopic bronchiectasis. The persistent hyperplastic thymus, generalized lymphoid hyperplasia, and hypoplasia of the aorta and adrenals suggested thymicolymphatic constitution. There was slight chronic cholecystitis, and the liver contained foci of leucocytes. The brain was not examined.

CASE 7.—A white man, aged 67 years, entered the hospital Aug. 1, 1938. He had been in good health until seven years previously, when he had a sudden attack of dyspnea which was relieved by adrenalin. Thereafter he had dyspnea when excited, and then upon moderate exertion; this increased in severity until finally he was short of breath at rest, and for the preceding few weeks he had been orthopneic. He spent the ten days before admission in a chair because of dyspnea, swelling of the legs, and sleeplessness. In four years he lost 65 pounds. There was no cough, wheezing, or chest pain.

Physical examination showed that the chest was emphysematous, with hyperresonance more pronounced on the right side. The breath sounds were absent over the right side of the chest, except in the interscapular region, where they seemed normal. There were râles at the base of the left lung. The heart was not definitely enlarged; the rate and rhythm were normal. There were no murmurs. The blood pressure was 180/106. The peripheral arteries were sclerotic. There was marked edema of the ankles.

Roentgenologic examination showed emphysema of the lungs, pneumothorax on the right, an old fibrotic scar at the left apex, and probably an inflammatory lesion at the right base. There was no abnormality of the heart or aorta.

The electrocardiogram on August 1 showed occasional auricular extrasystoles, but was normal in other respects. Digitalis was given in full doses. The patient had several attacks of auricular paroxysmal tachycardia, with partial A-V block (Fig. 7). Esophageal leads were employed to show the auricular deflections more clearly. The tachycardia was controlled only by fairly large doses of quinidine. The pneumothorax and edema cleared up satisfactorily, and the paroxysmal tachycardia did not return. The dyspnea upon slight exertion persisted. Upon one occasion tracings showed what was probably A-V nodal rhythm, with a rate of 88 per minute; the rhythm was regular, but no auricular waves could be identified.

CASE 8.—A white man, 53 years of age, entered the hospital Aug. 25, 1939. For the preceding eighteen months he had suffered from fatigue, shortness of breath, and swelling of the legs. For many years he had had a cough productive of yellowish sputum.

Physical examination showed emaciation, dyspnea, cyanosis, and pronounced edema of the feet, legs, and thighs. The lungs were resonant, but contained numerous crepitant and coarse râles throughout, and there were small areas of bronchovesicular breath sounds over the upper lobes. The heart was considerably enlarged, and there was a loud systolic murmur over the lower end of the sternum. The rhythm was regular except for occasional extrasystoles. The blood pressure was 110/78. The peripheral arteries were thickened. The liver was slightly enlarged.

Roentgenologic examination showed marked enlargement of the heart. In the lungs there were increased vascular shadows and also areas of inflammatory infiltration.

The electrocardiogram on August 26 showed normal rhythm, with occasional ventricular extrasystoles. There was right axis deviation, with inverted T waves in Leads II and III (Fig. 8, A). The patient was given digitalis in moderate amounts and improved temporarily, but there was no striking change at any time. On August 30 the electrocardiogram (Fig. 8, B) showed auricular paroxysmal tachycardia with an auricular rate of 188, and partial A-V block with a ventricular rate of 112. Later the rhythm became regular at a slower rate, and the curve of Sep-

tember 1 showed what was probably A-V nodal rhythm (Fig. 8, C), without any deflections which could be identified as P waves. The patient then grew gradually worse and died Sept. 5, 1939.

Autopsy showed bilateral sacular and tubular bronchiectasis and bronchiectatic abscesses. There were mucopurulent bronchitis and an old fibrous tuberculosis of the lungs and bronchial lymph nodes. The heart weighed 400 grams and showed right-sided dilatation. There were myocardial hypertrophy and brown atrophy. There were extensive subendocardial fibrosis and subepicardial fatty infiltration. There was minimal sclerosis of the coronary arteries and of the mitral and tricuspid valve leaflets.

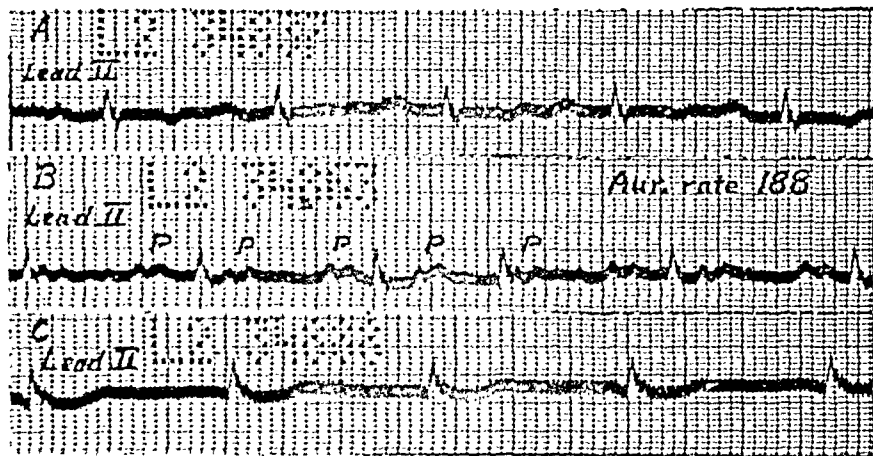


Fig. 8.—Case 8. A, Aug. 26, 1939. Lead II. Normal rhythm. Rate 107. B, Aug. 30, 1939. Lead II. Auricular paroxysmal tachycardia with partial A-V block, usually 2:1. Auricular rate 188. Had had digitalis. C, Sept. 1, 1939. Lead II. Probably A-V nodal rhythm. Rate 88. No auricular deflections visible.

CASE 9.—A white woman, 23 years of age, was followed closely throughout the winter of 1939-1940, during a pregnancy. She gave a history of rheumatic fever in childhood, but tolerated exertion fairly well. Examination showed very slight cardiac enlargement, a blowing systolic murmur at the base, a high-pitched diastolic murmur at the left sternal margin, and a low pitched diastolic murmur at the apex. The rate and rhythm were normal. The blood pressure was usually about 100/60. There were no signs of congestive failure.

The patient did well until March 7, 1940, when she developed acute edema of the lungs, from which she made a good recovery. On April 30, 1940, when almost at term, she was delivered of a normal infant by low Caesarean section, from which she recovered satisfactorily. Digitalis was continued in a dose of 0.1 Gm. daily. The cardiac rhythm remained normal throughout.

On July 18, 1940, she had a short attack of palpitation. On July 20 she developed shortness of breath and rapid, violent beating of the heart upon very slight exertion. Physical examination showed nothing new except slight cardiac irregularity and rather pronounced pulsation of the neck veins. The cardiac rate was 100. Upon rather mild exertion the rate rose to 210 and the rhythm was regular. The rate gradually fell to the previous level and slight irregularity returned. Pronounced but transient slowing was produced by carotid sinus pressure.

The electrocardiograms, which had previously shown normal rhythm, with broad, notched P waves (Fig. 9, A), now showed auricular paroxysmal tachycardia with an auricular rate of 195 (Fig. 9, B). There was high-grade partial A-V block, with a ventricular rate of 100. After exercise the auricular rate was 219. The

ventricles responded to each auricular beat for a short time (Fig. 9, *C*), then became slower and irregular, and finally displayed a long period of near standstill, interrupted by idioventricular beats (Fig. 9, *D* and *E*), at the end of which they resumed their previous rate of 100 per minute.

The dose of digitalis was increased for a few days, but the shortness of breath and palpitation continued, although they were less easily brought on. Quinidine was given and the patient tolerated moderate exertion without symptoms. The quinidine was stopped for a few days and the palpitation and shortness of breath returned. When quinidine was resumed the symptoms ceased. Since then quinidine has been taken irregularly. Tachycardia occurs every few days, often when quinidine has not been taken. Small amounts of quinidine are followed by normal rhythm in one or two hours.

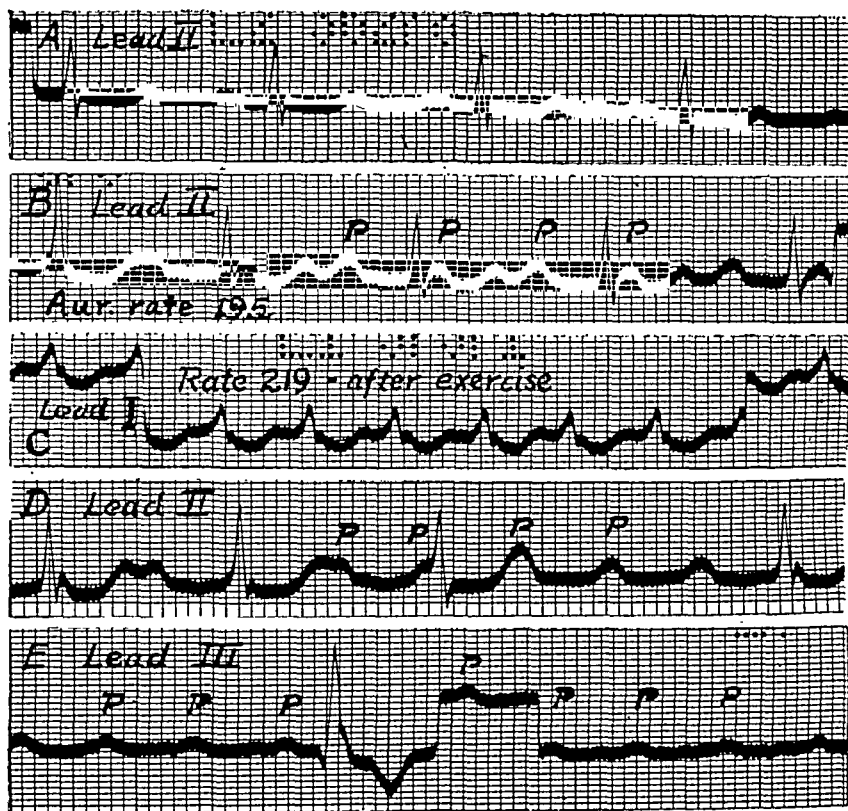


Fig. 9.—Case 9. *A*, March 12, 1940. Lead II. Normal rhythm, rate 90. *B*, July 20, 1940. Lead II. Auricular paroxysmal tachycardia, with partial A-V block. Auricular rate 195. Ventricular rate 100. Patient had had digitalis. *C*, *D*, and *E*, Leads I, II, and III, resp., July 20, 1940. After exercise, 1:1 ventricular response is followed by slowing and irregularity of the ventricles, with a period of ventricular near-standstill interrupted by idioventricular beats.

CASE 10.—A white man, aged 54 years, was first seen Feb. 14, 1940. His blood pressure had been somewhat elevated for about six years, but there had been no symptoms associated with his hypertension except nocturia. The patient considered himself in good health until Feb. 12, 1940, when he had an attack characterized by a feeling of numbness in the precordium, nausea, and profound weakness. There was no pain or shortness of breath. Examination showed that the patient was overweight. There was slight enlargement of the heart, but no murmurs. The rate was about 70, and there were frequent premature beats. The blood pressure was 150/125. The remainder of the examination was negative. The electrocardiogram (Fig. 10, *A*) showed frequent auricular extrasystoles and slight left axis deviation, with inverted T waves in Lead I. The precordial leads were normal

with the exception of inversion of the T waves in the lead taken in the left anterior axillary line. There were no further attacks of this type. He was given theophylline and digitalis. After digitalization the dosage of this drug was reduced to 0.1 Gm. daily, but in September he took 0.2 Gm. daily.

During the night of Sept. 21, 1940, he began having vague precordial discomfort, described as a sense of pressure or numbness or shakiness, and nausea and vomiting. There was no pain, shortness of breath, or edema. He was given digitalis (0.4 Gm.) on September 23. Physical examination on September 24 showed that the heart was slightly enlarged. The rate varied between 44 and 52 per minute. There were periods of bigeminy. At times there were numerous premature beats. At other times the rhythm was regular. The heart sounds varied in intensity when the ventricles were beating slowly and regularly. Pulsations in the neck veins were counted at approximately 200 per minute. The blood pressure was 164/120. The

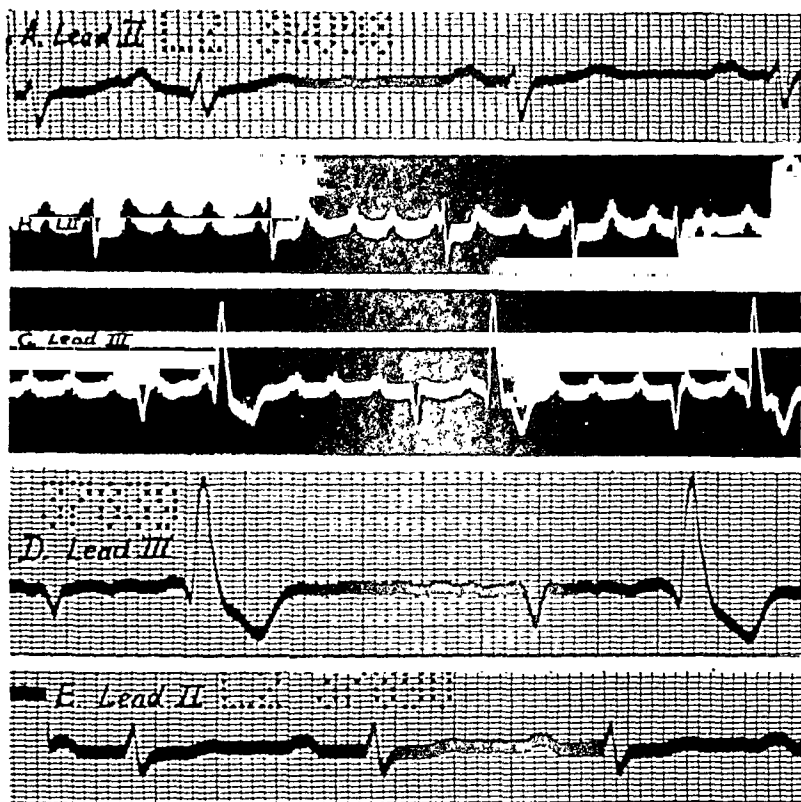


Fig. 10.—Case 10. *A*, Feb. 14, 1940. Lead II. Normal rhythm with auricular extrasystoles. P-R 0.20 sec. *B*, Sept. 24, 1940. Lead II. Auricular paroxysmal tachycardia with partial A-V block. Auricular rate 200. Ventricular rate 56. *C*, Sept. 24, 1940. Lead III. Auricular paroxysmal tachycardia with partial A-V block and extrasystolic bigeminy. Ventricular rate 58. In *B* and *C* the auricles are slightly irregular. Patient had been overdigitalized. *D*, Sept. 26, 1940. Lead III. Auricular fibrillation. Bigeminy. *E*, Oct. 2, 1940. Lead II. Normal rhythm. Prolonged P-R interval (0.28 sec.).

remainder of the examination was negative. The electrocardiograms showed auricular paroxysmal tachycardia with high-grade A-V block (Fig. 10, *B*). The auricular rate was 200, the ventricular rate, 56. There were ventricular extrasystoles and extrasystolic bigeminy (Fig. 10, *C*). Digitalis was stopped. Subsequent electrocardiograms showed auricular fibrillation (Fig. 10, *D*), and a few days later normal rhythm (Fig. 10, *E*). The patient dropped dead in December, 1941.

CASE 11.—A white man, 52 years of age, was admitted March 15, 1939, complaining of shortness of breath and swelling of the legs. These symptoms followed an acute respiratory infection which had occurred three weeks previously, and they became increasingly severe; the edema extended upward to include the abdomen. Examination showed that the heart was markedly enlarged; the rhythm was regular and the rate was 85. There were no murmurs. The blood pressure was 144/110. The arteries were not tortuous. There were dullness, diminished breath sounds, and râles at the bases of the lungs. The liver was enlarged and there was a little ascites. There was marked edema of the lower extremities, genitalia, and abdominal wall.

Roentgenologic examination showed marked enlargement of the heart.

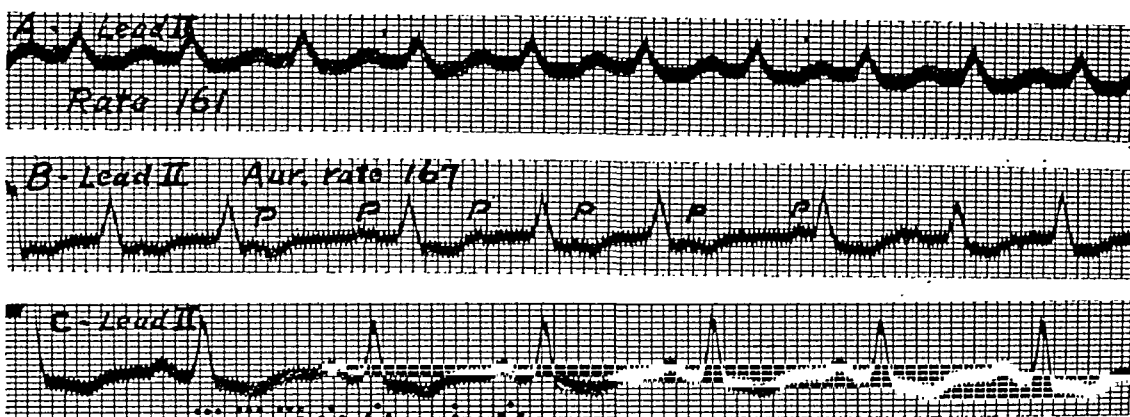


Fig. 11.—Case 11. A, March 18, 1939. Lead II. Paroxysmal tachycardia of supraventricular origin. Rate, 161. B, March 20, 1939. Lead II. After 2.4 grams of digitalis in 5 days. Auricular paroxysmal tachycardia with partial A-V block. Auricular rate 167, ventricular rate 131. C, March 21, 1939. Lead II. Normal rhythm, rate 107.

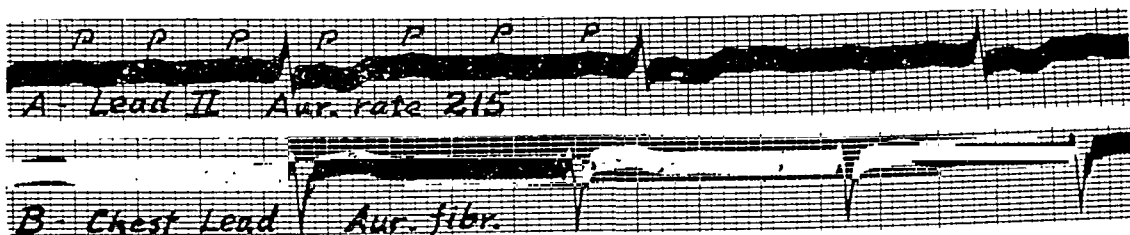


Fig. 12.—Case 12. A, Nov. 10, 1941. Lead II. Auricular paroxysmal tachycardia with 4:1 A-V block. Auricular rate, 215. B, Nov. 11, 1941. Precordial lead. Auricular fibrillation, ventricular rate 60.

On March 18 there occurred an attack of tachycardia which was shown by the electrocardiogram (Fig. 11, A) to be of supraventricular origin. The patient developed acute edema of the lungs, and the blood pressure rose to 170/120. He was almost moribund. By March 20 he had received 2.4 Gm. of digitalis in five days, and the tracing (Fig. 11, B) showed auricular paroxysmal tachycardia with partial A-V block. The auricular rate was 167, and the ventricular rate, 131, per minute. On the following day normal rhythm was present (Fig. 11, C). After this the patient improved remarkably; the blood pressure fell to 130/80 and the size of the heart returned almost to normal.

CASE 12.—A white man, aged 80 years, entered the hospital Nov. 8, 1941, because of urinary obstruction of three weeks' duration caused by benign enlargement of the prostate. He had suffered from shortness of breath for four years, and had been taking digitalis for three years. Examination showed evidence of senility

and emaciation. The heart was slightly enlarged and was irregular; the rate was 68. There were no murmurs. The blood pressure was 110/80. The peripheral arteries were thickened. The lungs were normal. The liver was not enlarged. There was edema of the left ankle which was attributed to varicose veins.

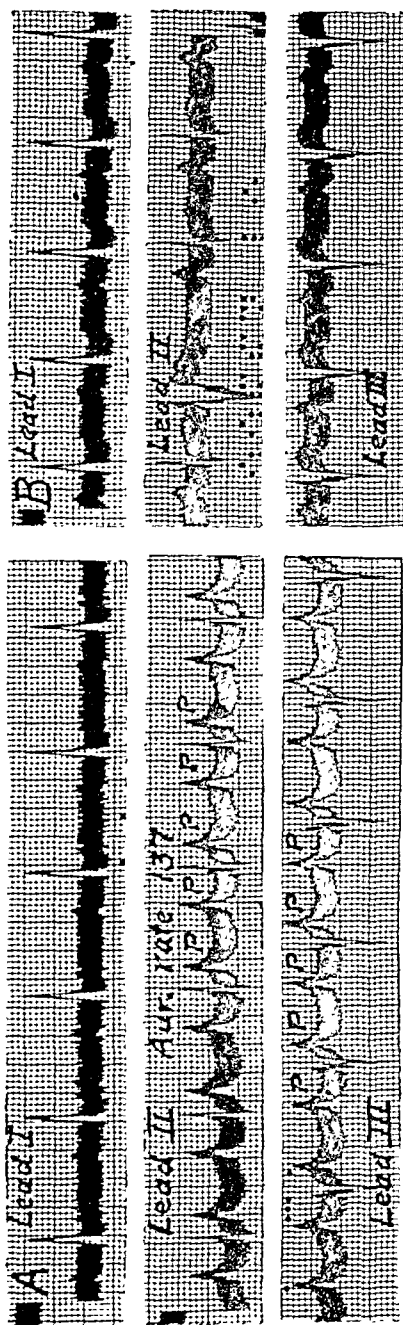


Fig. 13.—Case 13. A, May 25, 1935. Leads I, II, and III. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 137. B, May 27, 1935. Leads I, II, and III. Normal rhythm with ventricular extrasystoles and prolonged P-R interval (0.24 sec.).

Digitalis, in a dose of 0.5 Gm., was given November 9. On the following day the electrocardiogram (Fig. 12, A) showed auricular paroxysmal tachycardia with partial A-V block, usually 4:1, with an auricular rate of 215 and a ventricular rate of 55 per minute. On November 11 the tracing (Fig. 12, B) showed auricular fibrillation with a ventricular rate of 60. There were many idioventricular beats, indicating overdigitalization. Subsequently the patient had a transurethral resection of the prostate, from which he made a good recovery.

CASE 13.—A white man, 68 years of age, was examined May 24, 1935. He had been troubled with attacks of nausea and vomiting. Examination showed that the heart was of normal size, but irregular, with a rate of 68 per minute. The lungs were normal, and the abdomen was negative. There was no edema. An electrocardiogram on the following day (Fig. 13, *A*) showed auricular paroxysmal tachycardia with 2:1 A-V block. The auricular rate was 137, and the ventricular rate, 68, per minute. There were a few ventricular extrasystoles. On May 27 the rhythm was normal except for ventricular extrasystoles (Fig. 13, *B*). A few months later the patient developed cardiac failure, but the cardiac rhythm remained normal.

CASE 14.—A white woman, 17 years of age, was admitted Nov. 1, 1932. She gave a history of nervousness, weakness, fatigue, palpitation, and irregularity of the heart. These symptoms began in August, 1931, and improved temporarily under iodine therapy in January, 1932. Enlargement of the thyroid gland appeared at that time. The palpitation was described as forceful beating of the heart, and the irregularity as a skipping of beats. No attacks or paroxysms of tachycardia or irregularity were noticed.

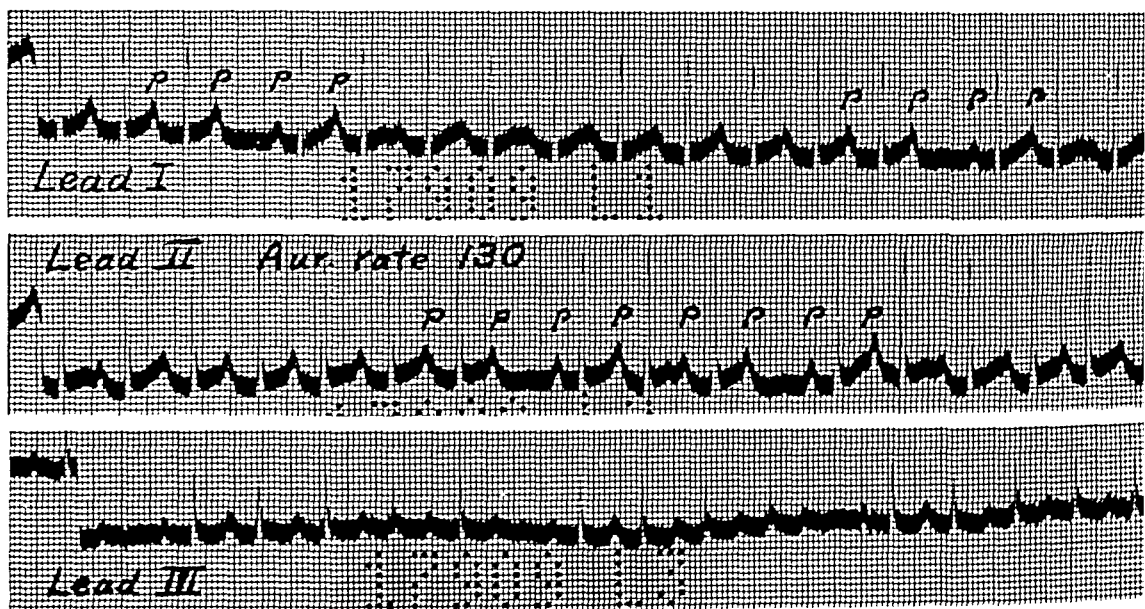


Fig. 14.—Case 14. Leads I, II, and III. Probably auricular paroxysmal tachycardia and partial A-V block with dropped beats. Auricular rate, 130.

Examination showed moderate enlargement of the thyroid, with a bruit over the gland. There were exophthalmos and a fine tremor of the fingers. The heart was normal in size, and there seemed to be numerous dropped beats. The rate was 108. There were no murmurs. The blood pressure was 135/78. There were no signs of congestive failure. The basal metabolic rate was plus 45 per cent. Roentgenologic examination showed no abnormality of the heart. The electrocardiogram (Fig. 14) showed an auricular rate of 130 and partial A-V block, with frequent dropped beats. Subsequently the rhythm seemed normal clinically, but no other electrocardiograms were taken. A subtotal thyroidectomy was followed by a good recovery. It is possible that this patient had auricular paroxysmal tachycardia with partial A-V block, but this is not certain.

CASE 15.—A white man, 64 years of age, was admitted Jan. 18, 1933. For four months he had suffered from attacks of rapid beating of the heart and shortness of breath; these lasted a few minutes and occurred several times a day. Exam-

nation showed that the patient was overweight. The heart was moderately enlarged, and there were faint systolic murmurs at the apex and base. The rhythm was irregular, and the rate was approximately 200 per minute. The blood pressure was 120, systolic. There were no signs of congestive cardiac failure. There were abrupt changes from tachycardia to normal rate, and from normal rate to tachycardia. The tachycardia was stopped by pressure upon the right carotid sinus, but soon returned. Many electrocardiograms were obtained, and showed a complicated arrhythmia. There were many brief attacks of tachycardia, apparently arising from two or more foci in the auricles, which had an abrupt onset and termination. There was also variation in the form of the ventricular deflections. In addition, there were brief periods of partial A-V block, as shown in Fig. 15. There were also premature ventricular deflections of abnormal outline, some of which probably were ventricular extrasystoles. Quinidine was given irregularly from January 21 to 24 without apparent benefit. Digitalization was begun on January 25 and completed on January 27, and then maintained by 0.1 Gm. daily. After this there were occasional auricular extrasystoles (Fig. 15, D), but no further attacks of tachycardia or dyspnea.

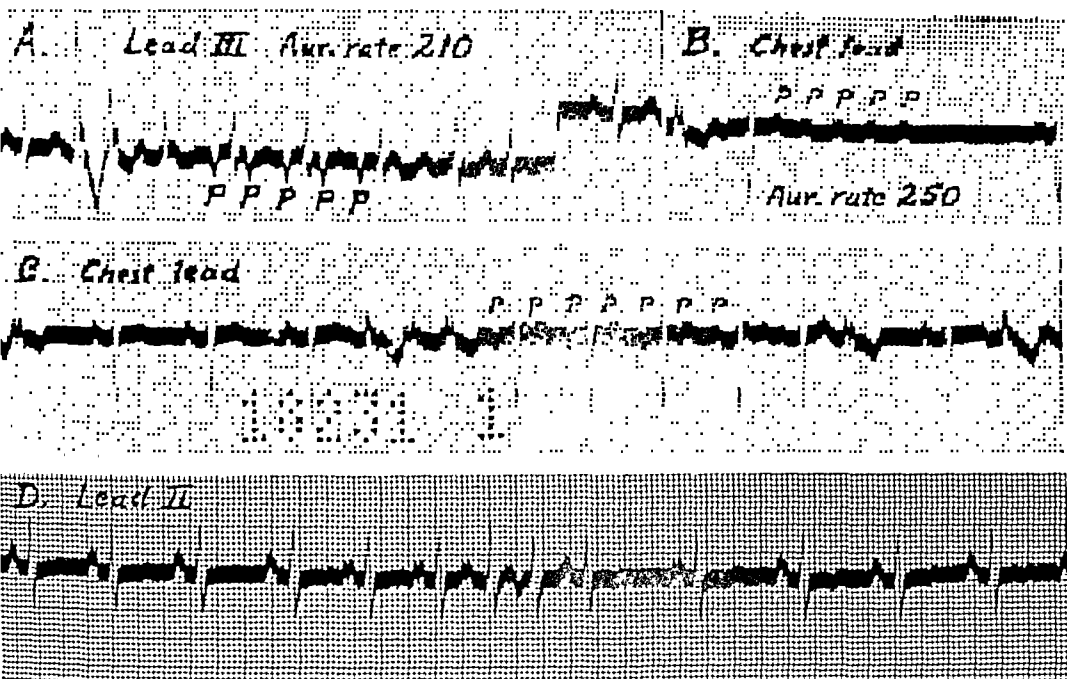


Fig. 15.—Case 15. A, Jan. 19, 1933. Lead III. A short paroxysm of tachycardia arising in at least two different foci in the auricles, and showing partial A-V block. Auricular rate 210. B, Jan. 21, 1933. Precordial lead. Unusual mode of termination of an attack; there is A-V block. Auricular rate 250. C, Jan. 21, 1933. Precordial lead. A short attack showing partial A-V block. Auricular rate approximately 200. D, Jan. 24, 1933. Lead II. Normal rhythm with auricular extrasystoles.

CASE 16.—A 26-year-old white woman entered the hospital March 13, 1929. For nearly a year she had suffered from shortness of breath, palpitation, swelling of the ankles, and nocturia. For the preceding month the swelling had been more extensive, involving the legs, thighs, and abdomen. There was no history of rheumatic fever.

Physical examination showed that the patient was dyspneic, orthopneic, and cyanotic. There was pronounced edema of both lower extremities, the right upper extremity, and the right breast. The heart was markedly enlarged. A systolic

murmur and gallop rhythm were present at the apex. No diastolic murmur was heard. The rhythm was regular, and the rate was 132 per minute. The blood pressure was 170/128. There were râles at the bases of the lungs. The liver and spleen were enlarged.

Roentgenologic examination showed marked cardiac enlargement and congestion of the lungs.

The electrocardiogram (Fig. 16, *A*) was taken March 16, 1929, after 1.8 Gm. of digitalis had been given. There was complete atrioventricular dissociation. The auricles and the ventricles were beating regularly and independently, the former at a rate of 160 and the latter at 84 per minute. No other electrocardiograms were obtained during this admission. The patient improved rapidly. Diuresis was accompanied by a loss of weight from 207 to 137 pounds. The blood pressure fell to 140/100, and the heart rate to 85.

The patient returned to the hospital July 31, 1931. Her symptoms and physical signs were essentially the same as on the previous admission. The blood pressure was 200/150. The heart rate varied from 90 to 75 per minute, and the electrocardiogram (Fig. 16, *B*) showed normal rhythm. In this curve the P waves are of different outline, as compared with the previous curve. The patient again improved.

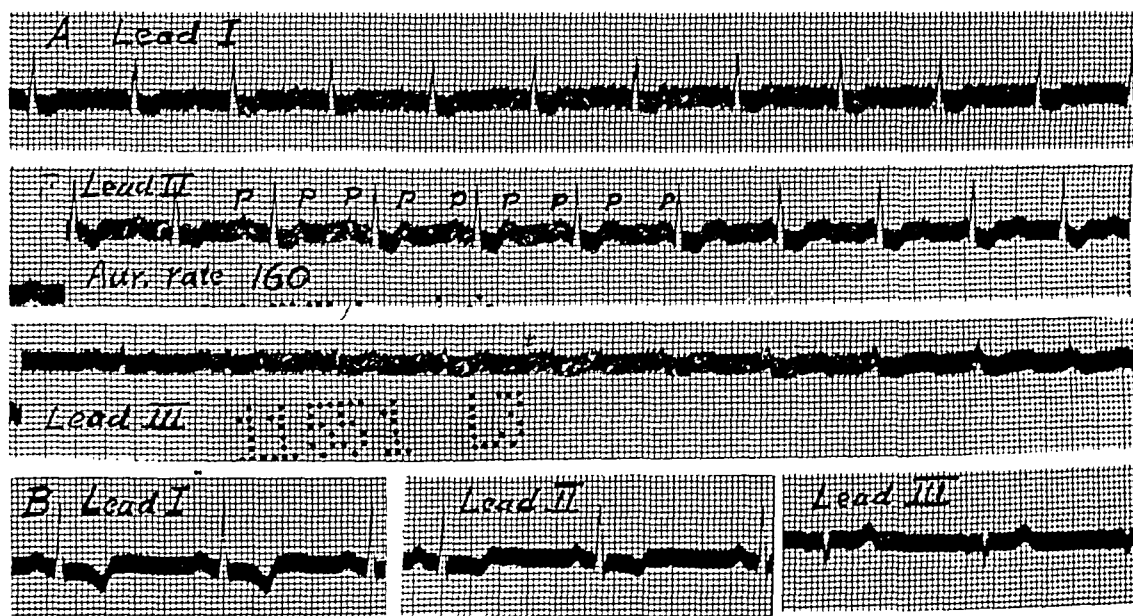


Fig. 16.—Case 16. *A*, March 16, 1929. Leads I, II, and III. Auricular paroxysmal tachycardia with complete dissociation. Auricular rate 160, ventricular rate, 84. *B*, Aug. 11, 1931. Leads I, II, and III. Normal rhythm.

CASE 17.—A 48-year-old white man entered the hospital May 12, 1942. He had felt well until one year previously. At that time he developed severe dyspnea during moderate exertion. It was relieved by morphine. His blood pressure was found to be 220. After that his pressure remained high, and he had headaches, blurred vision, and attacks of paroxysmal nocturnal dyspnea. Two months prior to admission his blood pressure was 240. A diagnosis of myocardial infarction was made by his physician. Since then he had been at rest in bed, and had taken digitalis regularly. There was no history of pain in the chest or edema of the extremities.

Physical examination showed an obese man who was dyspneic, orthopneic, and slightly cyanotic. The eye grounds showed evidence of retinal arteriosclerosis and

angiospasm. The heart was enlarged and was beating regularly at a rate of 120. The heart sounds were scarcely audible because of many coarse bubbling râles in the lungs. The blood pressure was 230/150. The peripheral vessels were not appreciably thickened. The liver was not enlarged. There was no edema of the extremities.

Shortly after admission, while being examined, the patient had an attack of acute pulmonary edema, from which he recovered after the administration of theophylline intravenously, and morphine, and phlebotomy, with the removal of 500 c.c. of blood, and the use of the oxygen tent. He was given 1.6 Gm. of digitalis in twelve hours, which caused nausea and vomiting. On the following day the patient was still somewhat dyspneic, and the blood pressure was 180/120. There was no pain in the chest. During the next few days the temperature rose to 99.6° F., the leucocyte count rose from 10,000 to 14,000 per c. mm., and the patient gradually improved. He was discharged May 26, 1942.

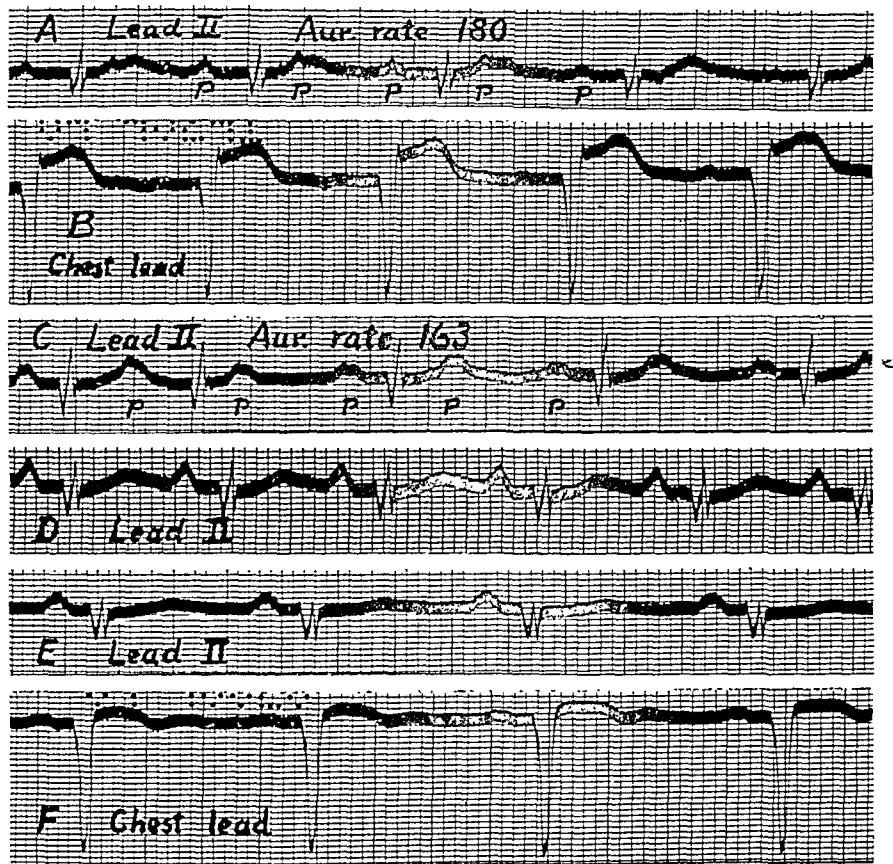


Fig. 17.—Case 17. *A*, May 13, 1942. Lead II. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate, 180. *B*, May 13, 1942. Precordial lead showing the changes of recent myocardial infarction. *C*, May 15, 1942, 2:15 P.M. Lead II. Auricular paroxysmal tachycardia with partial A-V block, usually 2:1. Auricular rate 163. Note the change in the form of the P waves. *D*, May 15, 1942, 4:50 P.M. Lead II. Normal rhythm. *E*, May 20, 1942. Lead II. Normal rhythm. Note the change in the form of the P waves. *F*, May 20, 1942. Precordial lead showing the expected progression of the changes accompanying myocardial infarction.

The first electrocardiogram (Fig. 17, *A*) was obtained May 13, 1942, the day after admission. It showed auricular paroxysmal tachycardia with 2:1 A-V block; the auricular rate was 180. Precordial leads showed changes suggesting very recent myocardial infarction (Fig. 17, *B*). On May 15, at 2:15 P.M. (Fig. 17, *C*), the auricular paroxysmal tachycardia was still present, with 2:1 A-V block most of the

time, and an auricular rate of 163. The auricular deflections were somewhat different in form from those of the previous curve. At 4:50 P.M. of the same day, normal rhythm was present, and the rate was 107 (Fig. 17, *D*). On May 20, 1942 (Fig. 17, *E*), normal rhythm was still present; the auricular deflections were different in form from those of the previous curve, and the rate was slower. Pre-cordial leads showed the expected progression of the changes of myocardial infarction (Fig. 17, *F*).

CASE 18.—A white man, 45 years of age, was a patient in the hospital from July 5 to 15, 1940. Four years previously he had experienced sudden, severe pain beneath the sternum which persisted for four hours and was relieved by morphine. After that he was subject to substernal pain upon slight effort. For about nine months he had been dyspneic upon mild exertion and sometimes at rest. The breathing was often noisy. Cough had been present for four months. He was found to be allergic to house dust and several other substances, and was given epinephrine by nebulizer and ephedrine by mouth. There had been no edema of the extremities. Examination showed slight cardiac enlargement, presystolic gallop rhythm, and many wheezing, musical, and crackling râles in the lungs. The blood pressure was 130/94. He was given rest and digitalis, and improved remarkably.

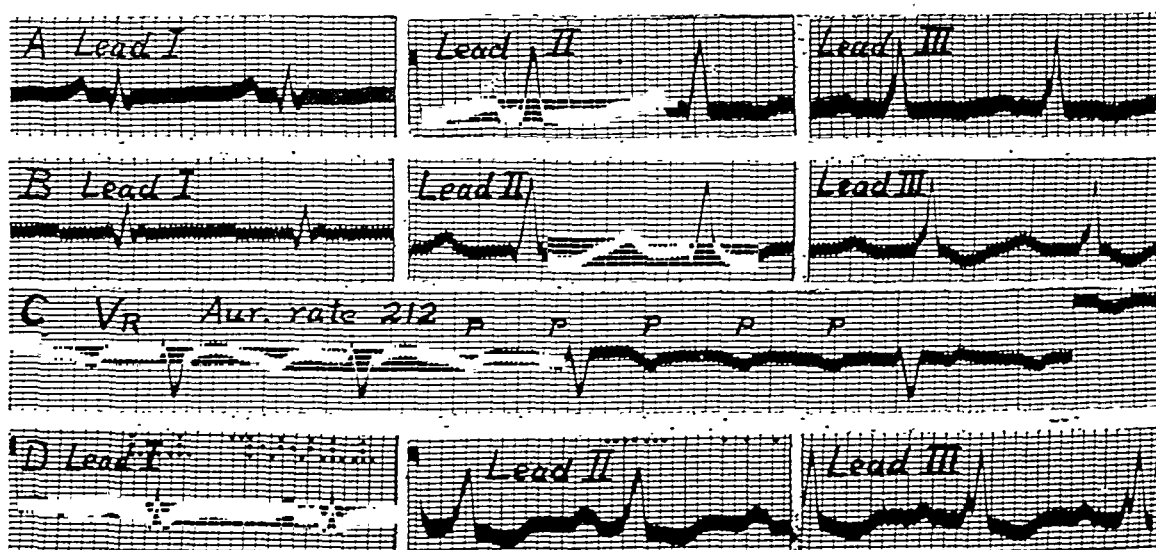


Fig. 18.—Case 18. *A*, July 6, 1940. Leads I, II and III. Normal rhythm. *B*, June 2, 1942. Leads I, II, and III. Auricular paroxysmal tachycardia with 2:1 A-V block. The auricular tachycardia is not readily apparent in these leads. *C*, June 2, 1942. Right arm potential (right arm electrode paired with the central terminal) taken a few seconds after *B*. The auricular tachycardia is clearly revealed during the short periods of 3:1 A-V block. *D*, June 9, 1942. Leads I, II, and III. Normal rhythm.

After being free from symptoms for six months, he began having shortness of breath again. In October, 1941, the substernal pain recurred, and thereafter orthopnea and edema of the ankles developed. He continued taking digitalis regularly. On May 25, 1942, he had an attack of tachycardia which was abrupt in onset and termination, lasted one hour, and was accompanied by substernal pain. He returned to the hospital June 1, 1942. Examination showed a dyspneic, apprehensive man with a severe, nonproductive cough. There were many musical and crepitant râles in the lungs. The heart was slightly enlarged, and gallop rhythm was present. The blood pressure was 152/118. There was slight edema of the ankles.

On the second hospital day (June 2, 1942), he developed tachycardia, accompanied by substernal pain. The heart rate was 160; it was slowed temporarily by pressure upon the left carotid sinus, but the tachycardia returned promptly upon cessation of the pressure. On June 4 the pulse was slower and the tachycardia had ceased after persisting for two days. There was, however, no other change in the patient's condition. He gradually improved.

The electrocardiograms on the first admission showed changes suggestive of old myocardial infarction (Fig. 18, *A*). On June 2, 1942, the curve showed auricular paroxysmal tachycardia with an auricular rate of 212 and partial A-V block, usually 2:1, sometimes 3:1 (Fig. 18, *B* and *C*). Normal rhythm was present on June 4 and persisted (Fig. 18, *D*).

COMMENT

Clinical Features.—Our interest in auricular paroxysmal tachycardia with A-V block was aroused by seeing 7 patients with this disturbance in the brief period of ten months, from October, 1937, to August, 1938. A review of 100 unselected cases of auricular paroxysmal tachycardia revealed 8 additional cases in which there was A-V block. The essential data in one additional case were supplied by Dr. John Parkinson (Case 1). The last 2 cases are of interest because of the associated myocardial infarction. In 8 of these 18 cases the tachycardia was the outstanding symptom, and in 5 it caused moderate to marked disability. In 4 other cases the tachycardia, although not the chief difficulty, was of importance in that it contributed to the disability of the patients. In the remaining 6 cases there was no disability, or the abnormal rhythm was merely an incident in the course of other more important conditions.

The degree of disability experienced by these patients is often greater than that which occurs with the common type of auricular paroxysmal tachycardia. In 29 cases it was possible to estimate the degree of disability. It was marked in 10, moderate in 7, and slight in 6. There was no apparent disability in 2, and in 4 others the abnormal rhythm was merely an incident of relatively minor importance in the course of some other illness. In general, the patients with organic heart disease and those with attacks of longer duration suffered more pronounced disability than the others (see Table I). Two patients developed acute edema of the lungs; both of these had organic heart disease. Another patient without organic heart disease died of cardiac failure caused by paroxysmal tachycardia which had been present almost continuously for three months.

In auricular paroxysmal tachycardia with A-V block, the duration of the attacks is often longer than in the common type of auricular paroxysmal tachycardia. Of the 17 previously reported cases, in 8 the attacks lasted several days; the longest was ninety-four days. Of our 18 patients, 13 had attacks lasting two days or longer. Three of these are known to have had attacks lasting twenty-six, sixty, and thirteen days, respectively. On the other hand, in 3 of the previous cases and in 3 of our own there were brief attacks which lasted only a few minutes.

The auricular rate is usually between 165 and 200 per minute.

Faster and slower rates sometimes occur. Four patients showed, at times, rates of 121, 120, 120, and 129 per minute, respectively. In one of these (Case 15) the slowing was caused by digitalis, and in another (Case 17) by assuming the recumbent posture, whereas in our Case 4 it was attributed to quinidine. Three of our other patients showed auricular rates of 136, 137, and 130 per minute, respectively, and in one of these the slowing was caused by quinidine (Case 6). Very rapid auricular rates are sometimes encountered. Lewis' patient¹ had a rate of 290 per minute. The first of the patients of Sprague and White⁶ showed a rate of 270 upon one occasion. Two of our patients had, at times, rates of 235 and 250 per minute, respectively. In some cases the auricular rate shows rather pronounced variations, usually in response to drugs.

The onset and termination of the abnormal auricular activity have been recorded graphically in several instances. They were abrupt, just as in paroxysmal tachycardia without A-V block. The case reported by Maddox¹¹ is exceptional in that the attack of tachycardia terminated by gradual slowing of the rate over a period of several days. In this and in many other respects it resembled that reported by Field, Barker, and Alexander.¹⁵

As a rule there is an abrupt transition from normal rhythm to paroxysmal tachycardia at the onset, and from paroxysmal tachycardia to normal rhythm at the termination of the attacks. In Dock's case,⁵ after 5 Gm. of digitalis in sixteen days, the mechanism changed to atrioventricular bradycardia with reciprocating rhythm. In Brown's patient,¹⁰ after large amounts of digitalis, the mechanism changed from auricular paroxysmal tachycardia to auricular fibrillation, and then to normal rhythm. One of our patients (Case 10) had auricular paroxysmal tachycardia with A-V block at a time when he was overdigitalized. Shortly after the digitalis was stopped the mechanism changed to auricular fibrillation, and then to normal rhythm (Fig. 10). Another patient (Case 12) was likewise overdigitalized when the paroxysmal tachycardia was present. On the following day the rhythm changed to auricular fibrillation, which persisted (Fig. 12). Although the transitions were not recorded, it seems highly probable that in these 3 cases the auricular paroxysmal tachycardia changed directly to auricular fibrillation without intervening normal rhythm. Spontaneous transitions from paroxysmal tachycardia to auricular flutter or fibrillation have been recorded, as have changes from flutter or fibrillation to paroxysmal tachycardia. Parkinson and Mathias¹⁶ observed a patient with auricular paroxysmal tachycardia whose rate increased progressively until there was a gradual transition to auricular flutter. Records were obtained by Carr¹⁷ on a patient with many short paroxysms of tachycardia arising in the A-V node who showed auricular flutter for a few seconds at the onset and termination of the attacks. This patient had received moderate amounts of digitalis. Lewis¹⁸ has reported a case

in which auricular fibrillation apparently changed to auricular paroxysmal tachycardia; the record of the transition was not published. It is possible that digitalis was responsible for the change to auricular fibrillation in the cases mentioned above, although in other cases of auricular paroxysmal tachycardia digitalis has restored normal rhythm without intervening auricular flutter or fibrillation.

In our Case 2 auricular flutter and auricular fibrillation were observed at different times, but it is not known whether there were transitions from either of these abnormal rhythms to paroxysmal tachycardia or vice versa. It is of interest that, of 100 unselected cases of auricular paroxysmal tachycardia, in only 5 was the patient known to have had auricular flutter or fibrillation, and that 3 of these had partial A-V block.

In some of the cases in which the onset or termination of an attack was recorded there was 1:1 ventricular response; the A-V block appeared during the course of the paroxysm. In other instances the block was present at the very beginning of the attack or continued to its very end.

In most cases the A-V block was fairly persistent or was maintained by digitalis, but 1:1 response could be brought on by exertion or occurred when digitalis was not taken. In some instances the patient was aware of the abnormal cardiac mechanism only during the periods of 1:1 ventricular response, which began and ended suddenly. The occurrence of 1:1 response increased the severity of the symptoms and accounted for the disability of some of the patients. Others, however, were incapacitated even with ventricular rates of about 100 per minute. In a few cases the block was transient and of short duration.

Patients with auricular paroxysmal tachycardia and partial A-V block are often very resistant to treatment. This is reflected in the long duration of some of the attacks. Pressure upon the carotid sinus restored normal rhythm only in Case 12 (Mackinnon). In many other cases it failed to do so. It commonly increased the degree of block and slowed the ventricles temporarily.

Digitalis was beneficial in 7 of the 17 previously reported cases; normal rhythm returned soon after the administration of full doses. In Cases 11 and 15 it was given without benefit, and, in the other 8 cases, it was apparently not used. Digitalis was given in 16 of our 18 cases, and in only 7 did it appear beneficial. In only 4 of these did normal rhythm return soon after the administration of the drug. In the other 3 it increased the degree of A-V block and prevented, in part, the occurrence of 1:1 response, so that the patients were improved symptomatically, but normal rhythm returned several days or weeks after full digitalization, and could not be attributed definitely to the drug. In some of the other cases digitalis may have been at least partly responsible for the partial A-V block, but did not appear to be beneficial in other respects. Digitalis sometimes causes considerable slowing of the auricular rate (Cases 4 and 14).

Quinidine was given in 5 of the previously reported cases. It prevented the attacks of paroxysmal tachycardia in Case 17 (Fine and Miller), but was without value in Cases 5, 6, 7, and 15. Quinine likewise was given in 5 of the previously reported cases. It restored normal rhythm in 3 (Cases 2, 8, and 10), but was without benefit in Cases 4 and 15. Quinidine was given to 8 of our patients. It restored normal rhythm in Cases 6, 7, and 9. In Cases 6 and 7, its continued use definitely prevented the return of the tachycardia, and in Case 9 it was probably of some benefit in preventing recurrences. In Cases 1, 2, 3, 4, and 15, quinidine was given without apparent benefit, although it slowed the auricular rate in Cases 3 and 4. There was no adequate explanation for death in Case 6; the patient had been taking quinidine sulfate in a dose of 0.3 Gm. 3 times daily for several days, but it is scarcely possible that this could have been responsible. Quinine was used in Case 2 without apparent benefit. Both quinidine and quinine sometimes cause conspicuous slowing of the auricular rate (Case 4 and our Cases 3, 4, and 6).

Mecholyl was given to 3 of our patients. It caused transient slowing of the ventricles by increasing the degree of block, but did not restore normal rhythm.

Electrocardiograms.—In the common type of auricular paroxysmal tachycardia the P waves are often almost indistinguishable because they are very small or flat, or because, in addition to being small, they fall upon some part of the ventricular complex. In about one-sixth of the cases the P waves are inverted. In only about 30 per cent are they upright and approximately similar in form to the P waves of normal rhythm. In auricular paroxysmal tachycardia with A-V block, about 60 per cent of the patients have P waves which are upright or largely so, and resemble, perhaps not exactly, but at least fairly closely, the P waves of normal rhythm. When P is diphasic or notched, it often shows a similar configuration during normal rhythm. The similarity of the P waves during the tachycardia and during normal rhythm is shown in 6 of the previously reported cases (Cases 3, 6, 7, 8, 9, and 15), and is well illustrated in ten cases of the present series (Cases 1, 2, 3, 5, 7, 10, 11, 13, 16, and 18). This indicates that in these cases the paroxysmal tachycardia had its origin near the sinoauricular node. It is possible that A-V block is more likely to occur in such cases, as compared with cases in which the form of P suggests an origin near the auriculoventricular node. In Cases 12 and 14 the P waves were upright during the tachycardia, but no tracings of normal rhythm were obtained for comparison. In 6 of the previously reported cases (Cases 2, 4, 5, 11, 14, and 17) and in 6 cases of our series (Cases 4, 6, 8, 9, 15, and 17) the P waves during the tachycardia were quite different from the P waves of normal rhythm. In Cases 4 and 8, P was very small during the tachycardia, whereas, in Cases 6 and 15, it was inverted. In Cases 9 and 17, the P waves were upright during the tachycardia but quite different in form from those of normal rhythm.

When the P waves are small or indistinct in the standard leads, it may not be possible to identify them with certainty, or to ascertain what type of arrhythmia is present. Under such circumstances it may be helpful to employ chest leads. By leading from two precordial contacts, one over the upper part of the sternum and the other over the ensiform, it is usually possible to record large auricular waves which are readily identified. This is well illustrated in Case 4 (Fig. 4). Esophageal leads may be even more helpful, for they invariably yield very large auricular deflections when employed as described by Brown.¹⁰ They may be especially helpful in distinguishing auricular paroxysmal tachycardia from flutter. In the former the auricular deflections are separated, during A-V block, by periods of electrical quiescence, in which the curve is at rest on the base line, whereas, in the latter, the curve is never at rest, but shows continuous changes in electrical potential (Figs. 2 and 7). These observations confirm those of Brown. The use of esophageal leads, however, imposes some hardship upon the patient.

The partial A-V block seems to be caused by the abnormally high auricular rate, at least to a considerable degree. In some of the patients, digitalis was a contributing factor. In none of the previously reported cases was there abnormal prolongation of the P-R interval during normal rhythm, although in several it was 0.20 second. In Case 2 (Singer and Winterberg), complete block persisted after the termination of the paroxysmal tachycardia. In the present series, likewise, the P-R interval was nearly always normal during normal rhythm, but there were a few exceptions. In Case 4 it was 0.22 second at times, but large amounts of digitalis had been given. In Case 10 the P-R interval was 0.20 second several months before the tachycardia occurred and before digitalis was given; when normal rhythm returned after the paroxysmal tachycardia it was 0.28 second, but the patient had been overdigitalized. One patient (Case 13) had a P-R interval of 0.24 second on the day when normal rhythm returned, and he had received no drugs; four months later it was 0.19 second.

The occurrence of auricular flutter and auricular fibrillation in Cases 2, 10, and 12 has been mentioned. Two other patients (Cases 7 and 8) showed abnormal auricular mechanism after cessation of the paroxysmal tachycardia; they yielded curves in which no auricular waves could be identified. It was thought that they might represent A-V nodal rhythm, but no special leads were employed and no large venous pulsations were observed, and it is possible that there was auricular standstill. The ventricles were beating regularly at normal rates. In several cases normal rhythm was disturbed by occasional auricular extrasystoles. One patient (Case 17) showed changes in the form of the P waves, both during the paroxysm of tachycardia and during normal rhythm shortly after the cessation of the attack.

The Mechanism of Auricular Paroxysmal Tachycardia.—Auricular paroxysmal tachycardia with partial A-V block resembles auricular flutter in many respects. It resembles flutter much more closely than does the common type of auricular paroxysmal tachycardia. The similarities extend beyond the presence of the partial block and the relatively long duration of some of the attacks. Quinidine and quinine often slow the auricular rate in auricular paroxysmal tachycardia and always do so in auricular flutter. In a few cases, digitalis in large amounts apparently converted auricular paroxysmal tachycardia into auricular fibrillation, a common occurrence in auricular flutter. In these cases, as in flutter, pressure upon the carotid sinus temporarily increases the degree of block and slows the ventricles, but almost never stops the attacks of abnormal rhythm. With respect to A-V block, the differences between auricular paroxysmal tachycardia and auricular flutter may be caused chiefly by the differences in the auricular rates in the two conditions.

In spite of the resemblances between auricular paroxysmal tachycardia with partial A-V block and auricular flutter, the two conditions differ from each other in several important respects. Digitalis sometimes slows the auricular rate in the former, whereas, in the latter, it has little effect, or induces auricular fibrillation. Pressure upon the carotid sinus restored normal rhythm in Case 13 (Mackinnon); it never does so in auricular flutter. In the common type of paroxysmal tachycardia, normal rhythm is often restored by pressure upon the carotid sinus. An important difference between auricular paroxysmal tachycardia with partial A-V block and auricular flutter is that in the former the auricular deflections are separated by periods of electrical quiescence, during which the curve is at rest on the base line, whereas, in the latter, the curve is never at rest, but shows continuous changes in electrical potential. This is apparent quite commonly in standard leads, usually in precordial leads, and always in esophageal leads.

If auricular paroxysmal tachycardia is caused by re-entry of the impulse, it must be a special kind of circus rhythm, differing from that of auricular fibrillation. Circus rhythm involving as part of the path of the circulating excitation wave either the sinoauricular node or the auriculoventricular node could account for most, if not all, of the features of auricular paroxysmal tachycardia. This possibility has been discussed briefly by Ashman and Hull.¹⁹ In our opinion, circus rhythm can account for auricular paroxysmal tachycardia only if it involves one of the nodes, or if the amount of muscle in some part of the main circus path is so small that its action potential cannot be recorded by ordinary methods. In a subsequent communication we hope to present additional evidence bearing upon this problem, and to discuss it at greater length.

SUMMARY

1. Seventeen previously reported cases of auricular paroxysmal tachycardia with auriculoventricular block are reviewed, and eighteen additional cases are reported.

2. This arrhythmia may occur at almost any age, and in persons with otherwise normal hearts or with organic heart disease.

3. The attacks are often of long duration, i.e., they commonly last several days or longer.

4. High-grade disability is common in patients with organic heart disease, but sometimes occurs in those with otherwise normal hearts. One patient without significant organic heart disease died of cardiac exhaustion and failure attributable entirely to the long continued tachycardia.

5. In some cases the auricular deflections of the electrocardiogram are small or not readily apparent in limb leads. In such instances precordial or esophageal leads are especially valuable because they yield prominent auricular waves and thus permit the identification of the arrhythmia. Such curves are quite different from those of auricular flutter, in that the auricular deflections are separated by periods of electrical quiescence, with the curve at rest on the base line.

6. Digitalis in large amounts often restores normal rhythm. Quinidine and quinine are somewhat less effective, but sometimes restore normal rhythm, occasionally even when digitalis has failed to do so. Pressure upon the carotid sinus rarely terminates the paroxysms; it was successful in only one case (Mackinnon⁹). Mecholyl and acetylcholine have been ineffectual. Some patients may not respond to any of these measures; in one such instance normal rhythm returned spontaneously after a period of rest in bed, whereas, in another, death resulted from cardiac exhaustion caused by the prolonged tachycardia.

7. Auricular paroxysmal tachycardia with partial A-V block resembles auricular flutter in many respects, but differs from it in some important particulars. Most of the features of auricular paroxysmal tachycardia can be accounted for by circus rhythm involving either the sinoauricular node or the auriculoventricular node.

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AURICULAR PAROXYSMAL TACHYCARDIA WITH ALTERNATION OF CYCLE LENGTH

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THE purpose of this paper is twofold: first, to describe an irregularity of the heartbeat which occurred during attacks of auricular paroxysmal tachycardia and was characterized by alternation of the cycle length, and, second, to discuss its significance with reference to the mechanism of auricular paroxysmal tachycardia.

As a rule, auricular paroxysmal tachycardia displays a high degree of regularity. This has been emphasized by Feil and Gilder,¹ who measured 11 to 18 consecutive ventricular cycles in the electrocardiograms of eight patients with auricular paroxysmal tachycardia. The maximal variation in the length of the ventricular cycles, not necessarily consecutive, ranged in different cases from 0.0071 to 0.0358 second, and was usually less than 0.0099 second; the average never exceeded 0.01 second. Two of their patients showed very slight alternation in the lengths of the cycles, but they did not comment upon this. Their measurements, in seconds, were as follows: Case R 742 (rate, 214 per minute), 0.2836, 0.2810, 0.2833, 0.2770, 0.2813, 0.2808, 0.2838, 0.2798, 0.2848, 0.2828, 0.2801, 0.2788, 0.2770, 0.2813, 0.2851, and 0.2752. Case G. 1843 (rate, 185 per minute), 0.3161, 0.3278, 0.3132, 0.3345, 0.3126, 0.3434, 0.3076, 0.3293, 0.3273, 0.3328, 0.3242, 0.3311, 0.3138, 0.3343, 0.3095, 0.3331.

In an interesting case reported by White² there were many short attacks of auricular paroxysmal tachycardia, with abrupt onset and termination, but with acceleration at the beginning and slowing toward the end of the paroxysms. During the tachycardia the P wave resembled the P of normal rhythm; it was upright in Lead II. The author did not comment on the alternation of cycle length shown by his measurements, which were as follows: (a) beginning of attack—0.407, 0.425, 0.384, 0.323, 0.316, 0.325, 0.308, 0.327, 0.317, 0.336, and 0.316 second; (b) at height of paroxysm—0.316, 0.323, 0.310, and 0.326 second (rate, 188).

Strong and Levine³ have emphasized the regularity of auricular paroxysmal tachycardia as contrasted with the irregularity of ventricular paroxysmal tachycardia. They measured the ventricular cycles during an attack of auricular paroxysmal tachycardia which occurred in one of their patients. The heartbeat was regular to a very high

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TABLE I
THE ESSENTIAL FEATURES OF CASES OF AURICULAR PAROXYSMAL TACHYCARDIA WITH ALTERNATION OF CYCLE LENGTH

CASE	AGE	SEX	FORM OF P WAVE*			MAXIMUM VARIATION† (SECONDS)	MAXIMUM VARIATION IN CONSECUTIVE CYCLES† (SECONDS)	RATE	CLINICAL DIAGNOSIS
			LEAD I	LEAD II	LEAD III				
Feil and Gilder ¹						0.008	0.006	214	
White ²	21	M	+	+	+	0.036	0.036	185	No organic heart disease
Strong and Levine ³			inverted (lead not stated)			0.028	0.019	188	
1	52	M	±	-	-	0.054	0.054	114	Arteriosclerosis, aortic stenosis, congestive failure
2	19	M	-	+	+	0.095	0.095	136	No organic heart disease
3	37	M	±	±	±	0.049	0.048	184	Mitral stenosis and aortic regurgitation
4	61	F	±	±	±	0.036	0.025	175	Hypertension, congestive failure
5	70	M	±	±	±	0.056	0.051	132	Arteriosclerosis
6	36	F	±	±	±	0.038	0.034	195	No organic heart disease
7	19	M	±	±	±	0.028	0.022	158	No organic heart disease
8	79	M	±	±	±	0.022	0.022	120	Hypertension, arteriosclerosis, cardiac enlargement
9	40	F	±	±	±	0.022	0.021	222	Hyperthyroidism, diabetes mellitus
10	46	M	±	±	±	0.036	0.024	150	No organic heart disease

*Upright, +; inverted, -; diphasic or intermediate, ±.

†The irregularity which sometimes occurred at the beginning and ending of attacks is not included.

In our Cases 1 and 2 the figures are for the auricular cycles, and, in all other cases, ventricular cycles.

degree, but there was a short period of slight alternation in cycle length which they did not mention or discuss. Their measurements, in seconds, were as follows: 0.41, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.41, 0.405, 0.41, 0.41, 0.41, 0.405, 0.41, 0.40, 0.41, and 0.405 (rate, 148).

Katz⁴ recently published a short record in which he called attention to alternation in length of auricular and ventricular cycles and P-R intervals. The longer ventricular cycles accompanied the longer auricular cycles, and the P-R intervals were longer after the shorter auricular cycles. Measurements of the tracing and clinical data were not given.

Mackinnon⁵ has pointed out that, in auricular paroxysmal tachycardia, the heartbeat is often somewhat irregular, but in none of his fifteen cases was there alternation of cycle length.

Careful inspection of the electrocardiograms in one hundred unselected cases of auricular paroxysmal tachycardia from our files revealed ten cases in which there was, in some of the curves, a slight irregularity of a type characterized by alternation in the lengths of the cycles. This irregularity, although slight, was apparent to the unaided eye. Its presence was confirmed by accurate measurements with a Lucas comparator. In only two of our cases were the auricular deflections sufficiently sharp to permit accurate measurements of the P-P intervals. In these the auricular cycles, the ventricular cycles, and the P-R intervals were measured. In the remaining cases only the ventricular cycles were measured. In all instances the beginning of the R wave and, in the two cases in which there were sufficiently sharp auricular deflections, the beginning of the P wave were the points employed in making the measurements. The essential features of our cases, and of those discovered in the literature, are given in Table I.

CASE REPORTS

Case 1.—A white man, 52 years of age, was first seen Jan. 27, 1933. He had advanced arteriosclerosis, aortic stenosis, and pronounced cardiac enlargement. He improved temporarily, but later his symptoms progressed and he developed angina pectoris of effort, attacks of tachycardia, pulsus alternans, and, finally, congestive cardiac failure. He died April 5, 1936. The autopsy showed advanced atherosclerosis, with calcification of the aorta, aortic stenosis with calcification, pronounced cardiac hypertrophy (the heart weighed 890 grams), and chronic passive congestion of the lungs and abdominal viscera. An electrocardiogram taken when the rhythm was normal is shown in Fig. 1, and an attack of auricular paroxysmal tachycardia is illustrated in Fig. 2. The measurements of the auricular and ventricular cycles and of the P-R intervals are given in the same figure. Although the patient had previously shown pulsus alternans, no alternation in the force of the pulse was observed at the time of the attack of paroxysmal tachycardia. The alternation in cycle length was not obvious on auscultation.

Case 2.—A 15-year-old boy was first seen in June, 1926, because of attacks of tachycardia. These continued to occur from time to time, and he returned to the clinic at intervals until July, 1935. Repeated examinations revealed no evidence of organic heart disease. A number of electrocardiograms were taken. Some of these were entirely normal. Others showed auricular extrasystoles. Still other curves

displayed auricular paroxysmal tachycardia which was sometimes of short, at other times of longer, duration. The paroxysm depicted in Fig. 3 occurred Sept. 12, 1930. The measurements of the auricular and ventricular cycles and of the P-R intervals are given in this figure. The alternation of cycle length is complicated by the occasional occurrence, usually every fourth beat, of an especially short cycle, which does not, however, interrupt the alternation.

In these two cases the auricular cycles, the ventricular cycles, and the P-R intervals alternated in length. The longer ventricular cycles corresponded to the longer auricular cycles, and the longer P-R intervals usually, but not invariably, followed the shorter auricular cycles. Because of the alternation of the P-R intervals, the R-R intervals varied less than the P-P intervals.

In the remaining cases the auricular deflections were not sufficiently sharp to permit accurate measurement; only the ventricular cycles were measured.

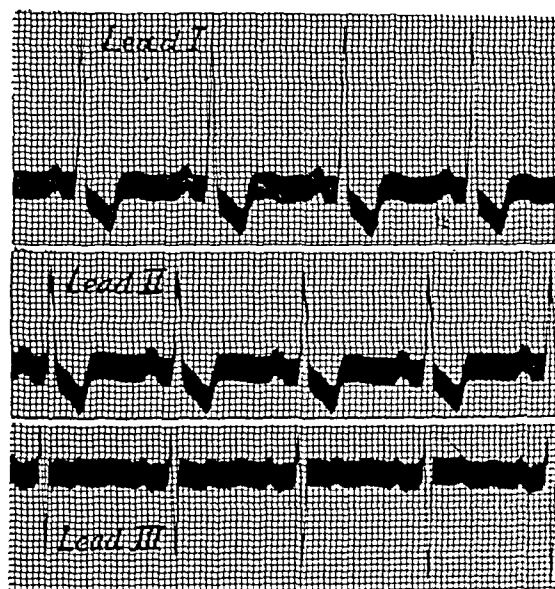


Fig. 1.—Case 1. Leads I, II, and III. Normal rhythm.

Case 3.—A white man, 37 years of age, was first seen Feb. 26, 1929. He had rheumatic heart disease, with mitral stenosis, aortic regurgitation, and cardiac enlargement. He complained chiefly of attacks of tachycardia, but also suffered from shortness of breath and occasional swelling of the ankles. The attacks of tachycardia were not stopped or prevented by quinidine, nor were they favorably influenced by thyroidectomy, which was performed because of mild hyperthyroidism. Digitalis in full doses apparently prevented the attacks for a year, but they returned. Two attacks were stopped by quinine intravenously, others by pressure upon the carotid sinus. Finally, the patient developed auricular fibrillation and severe cardiac failure, and died June 19, 1931. There was no autopsy. Many electrocardiograms were obtained, some during normal rhythm and others during paroxysms of auricular tachycardia. In one of these there was alternation of cycle length (Fig. 4). In this case, too, the variation in cycle length was complicated. The alternation of long and short cycles was interrupted by cycles of intermediate length which usually occurred every fifth beat, following the shorter, and preceding the longer, cycles.

Case 4.—The patient was a white woman, 61 years of age, with a blood pressure of 220/120, hypertensive heart disease, cardiac enlargement, and congestive failure. She grew progressively worse, and died two weeks after admission. The autopsy

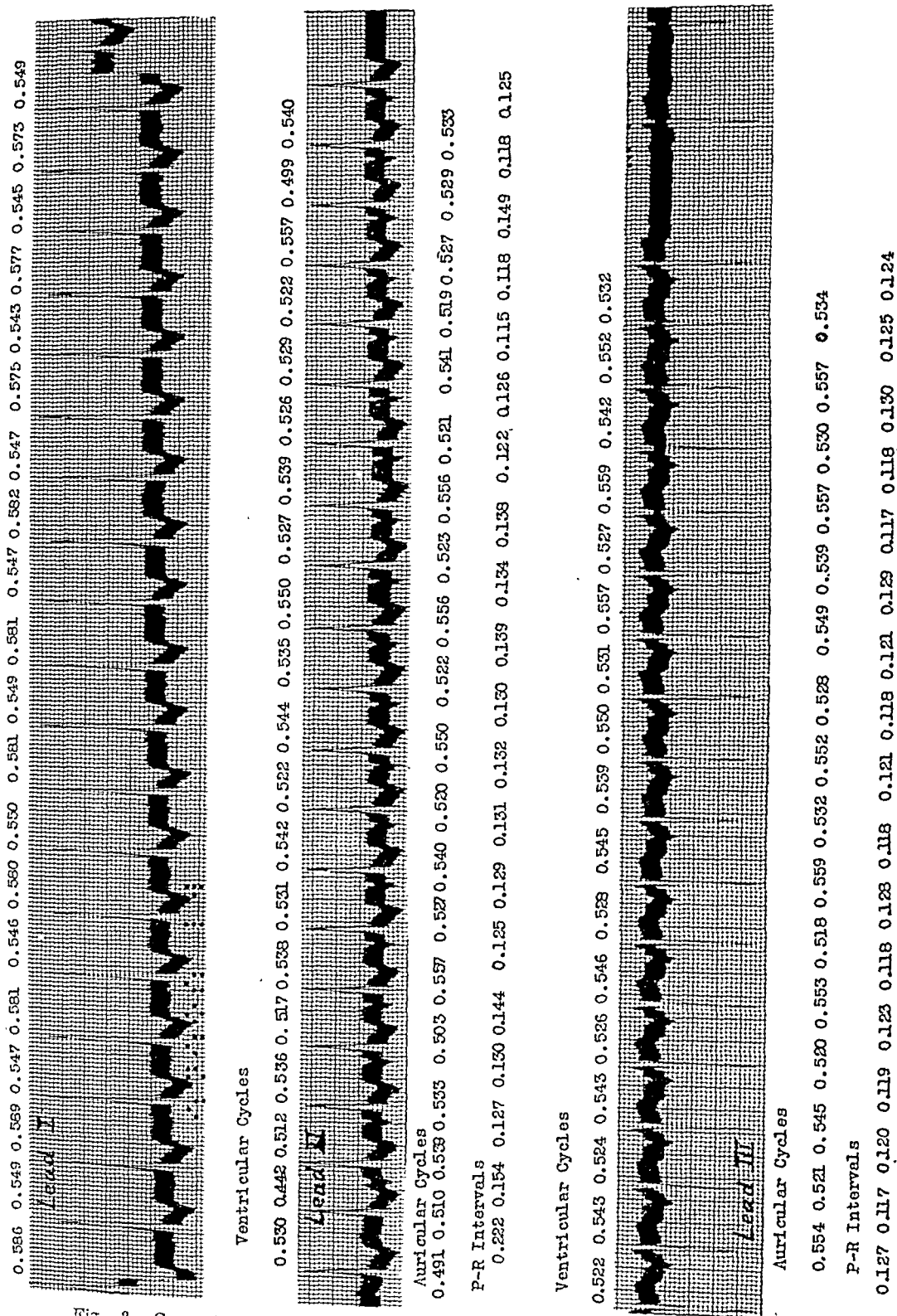


FIG. 2.—Case 1. Three standard leads. Auricular paroxysmal tachycardia. Measurements in seconds. In Lead I the ventricular cycle lengths are shown above; the auricular deflections are not sufficiently sharp to permit accurate measurements. Lead II shows one short paroxysm in its entirety. Lead III shows the end of a paroxysm. These curves show alternation in the lengths of the auricular and ventricular cycles and the P-R intervals.

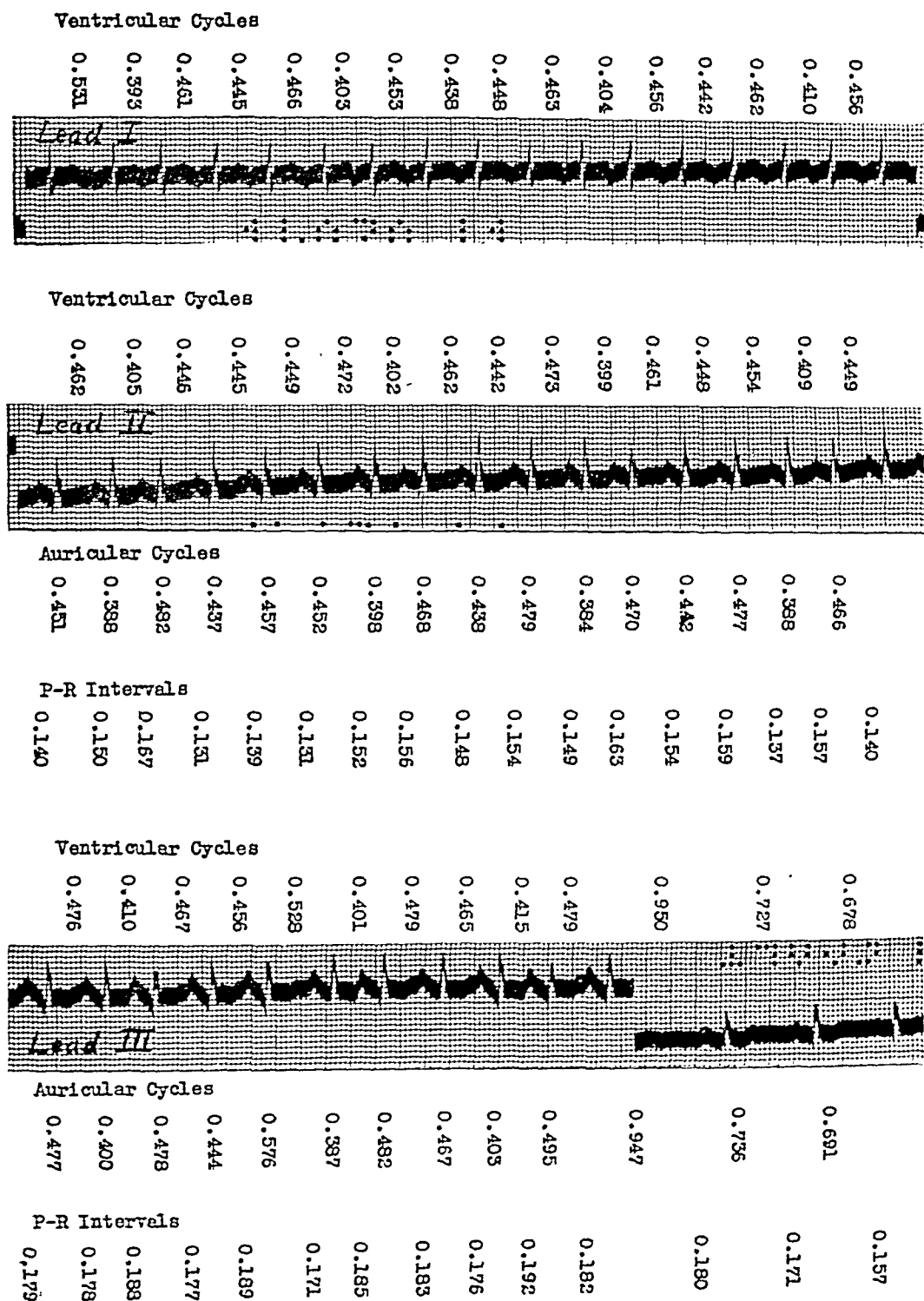


Fig. 3.—Case 2. Leads I, II, and III. Auricular paroxysmal tachycardia. Measurements in seconds. In Lead I the auricular deflections are not sufficiently sharp to permit accurate measurement. Lead III shows the termination of an attack. There is alternation in the lengths of the auricular and ventricular cycles and the P-R intervals.

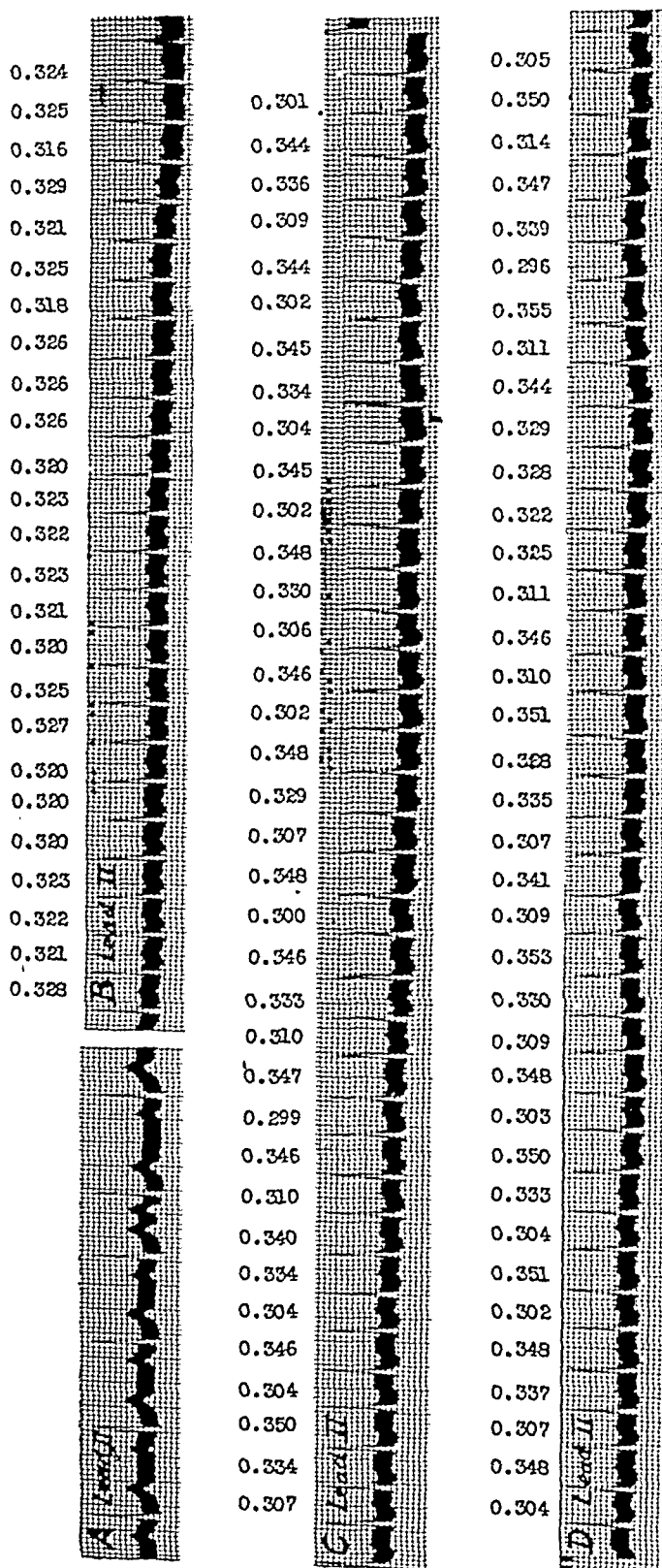


Fig. 4.—Case 3. Lead II. Ventricular cycle lengths, in seconds, are shown above the curves. The auricular deflections are not sufficiently sharp to permit accurate measurements. *A*, Normal rhythm with one auricular extrasystole. *B*, Auricular paroxysmal tachycardia, several hours after the onset of the attack. There is only transient, slight alternation of cycle length. *C*, Same attack six hours later. Alternation of cycle length is present. *D*, Same attack two minutes later, during the intravenous administration of 0.5 Gm. of quinidine dihydrochloride. In *C* and *D* the alternation of cycle length is apparent; it is interrupted by occasional cycles of intermediate length, usually every fifth cycle.

showed advanced atherosclerosis, with calcium deposits in the aorta, cardiac hypertrophy (the heart weighed 410 grams), and chronic passive congestion of all organs. The only electrocardiogram which was obtained showed auricular paroxysmal tachycardia, a rate of 175, and alternation of cycle length. The alternation was interrupted by an extra long cycle at times, usually every fifth beat. The measurements of the cycle lengths, in seconds, are as follows: 0.324, 0.342, 0.338, 0.344, 0.352, 0.334, 0.343, 0.341, 0.345, 0.346, 0.345, 0.355, 0.335, 0.360, 0.346.

Case 5.—The patient was a 70-year-old white man who suffered from palpitation of the heart and shortness of breath upon slight exertion. He was overweight, but examination of the heart revealed no abnormality other than an arrhythmia. On auscultation this appeared to be caused by several extrasystoles in succession, followed by an abrupt change in rate from 80 to 146, with regular rhythm. Pressure upon the carotid sinus caused only slight slowing. Later, another attack of tachycardia was terminated by carotid sinus pressure. The electrocardiogram showed auricular paroxysmal tachycardia, with alternating long and short cycles. The variations in cycle length were sometimes very slight, and, at other times, quite pronounced; the alternation, however, was maintained. The measurements, in seconds, of the cycle lengths in one complete paroxysm from beginning to end are as follows: 0.394, 0.551, 0.432, 0.450, 0.455, 0.461, 0.447, 0.464, 0.447, 0.473, 0.444, 0.469, 0.441, 0.468, 0.447, 0.463, 0.456, 0.469, 0.442, 0.462, 0.436, 0.466, 0.441, 0.460, 0.437, 0.457, 0.432, 0.449, 0.434, 0.452, 0.428, 0.455, 0.427, 0.445, 0.425, 0.446, 0.431, 0.445, 0.423, 0.444, 0.418, 0.452, 0.417, 0.441, 0.429, 0.443, 0.414, 0.446, 0.428, 0.453, 0.413, 0.464, 0.419, 0.453, 0.426, 0.450, 0.422, 0.460, 0.421, 0.459, 0.418, 0.462, 0.421, 0.435, and 0.425.

Case 6.—A white woman, 36 years of age, was first seen in January, 1926. Since the age of 5 years she had suffered from attacks of tachycardia during which the heart beat regularly at rates varying from 184 to 214 per minute. The attacks lasted from a few seconds to twelve days, and occurred at intervals of a few minutes to three weeks. They were accompanied by a sensation of throbbing of the heart, shortness of breath and nervousness, and, when long continued, by abdominal discomfort, nausea, and vomiting. She sometimes fainted at the onset or at the termination of an attack. Between attacks the heart was often slow, and sometimes irregular. Examination showed frequent extrasystoles, but no other cardiac abnormality. The blood pressure was 120/80. The patient was seen a number of times during the next eleven years. Some of her attacks were stopped by pressure upon the carotid sinus, others by mecholyl. Digitalis and quinidine were given without benefit. During normal rhythm there were many ventricular extrasystoles. In one attack of auricular paroxysmal tachycardia the electrocardiogram showed alternation of cycle length. There was considerable variation of the R-R interval at the onset of the attack, and alternation did not appear for several beats. The measurements, in seconds, from the beginning of the paroxysm are as follows: 0.435, 0.285, 0.301, 0.303, 0.300, 0.302, 0.307, 0.304, 0.313, 0.305, 0.319, 0.305, 0.335, 0.307, 0.327, 0.301, 0.335, 0.308, 0.339, 0.309, 0.339, 0.308, 0.335, 0.317, 0.330, 0.314, 0.331, 0.317.

In the remaining cases there was considerable variation in the cycles, but no definite disturbance in the alternation of their lengths.

Case 7.—A 19-year-old white man was referred for an electrocardiogram only. No history was obtained and he was not examined. A year later, however, when he had measles, examination revealed no abnormality of the heart. The electrocardiogram (Fig. 5) showed paroxysmal tachycardia of supraventricular origin, with alternation of cycle length. The onset and termination of an attack were recorded. The tracing was exceptional in that the P waves of Lead III appeared to alternate in form. The possibility cannot be excluded that this was caused by

alternation in the form of the T waves. This possibility received some support from the presence of alternation in the amplitude of the R waves in Lead II, although there was no alternation in the form of the T waves in that lead or in the amplitude of the R waves in Lead III.

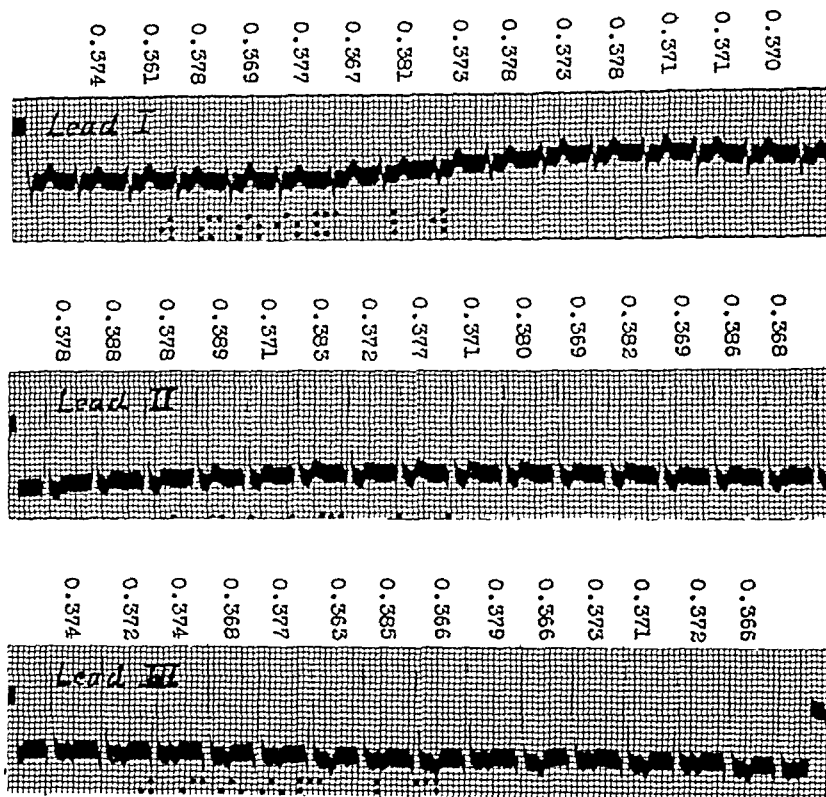


Fig. 5.—Case 7. Three standard leads. Auricular paroxysmal tachycardia, with alternation of ventricular cycle length. Measurements in seconds. There appears to be alternation in the form of the auricular deflections in Lead III.

Case 8.—The patient was a white man, 79 years of age. He had urinary obstruction caused by carcinoma of the prostate, and also hypertension (195/90), arteriosclerosis, cardiac enlargement, and mild congestive failure. He was observed to have many short attacks of tachycardia, with regular rhythm, and a rate of about 120 per minute. During the attacks there was pulsus alternans; alternate beats raised the systolic blood pressure to 150 and 130, respectively. Alternation of the cycle length was not detected clinically. The attacks were abrupt in onset and termination, and some of them were stopped by pressure upon the carotid sinus. Digitalis had no effect upon the attacks, but quinidine prevented them. Electrocardiograms showed paroxysmal tachycardia of supraventricular origin, of which there were sometimes many short attacks. When sinus rhythm was present auricular extrasystoles often occurred. During one attack of tachycardia there was alternation of cycle length; the measurements, in seconds, are as follows: 0.498, 0.506, 0.499, 0.516, 0.501, 0.515, 0.501, 0.515, 0.499, 0.517, 0.503, 0.518, 0.496, 0.517, 0.497, 0.514, 0.504, 0.517, 0.499.

Case 9.—The patient was a 40-year-old white woman who had had a goiter for seventeen years, symptoms of hyperthyroidism for two years, and diabetes for three months. She was undernourished and there was moderate, diffuse enlargement of the thyroid. There was no apparent abnormality of the heart. While the diabetes was being brought under control, hypoglycemia occurred, and epinephrine (1:1000,

0.6 c.c.) was given subcutaneously. After this an attack of tachycardia occurred. The electrocardiogram showed auricular paroxysmal tachycardia, with a rate of 222 and alternation of cycle length. The attack was stopped by pressure upon both eyes. A month later a typical paroxysm, with a heart rate of 188, occurred spontaneously; it lasted thirty minutes. In the curve which showed alternation of cycle length, measurements of the ventricular cycles gave the following values, in seconds: (Lead I) 0.263, 0.278, 0.264, 0.281, 0.265, 0.277, 0.266, 0.273, 0.271, 0.276, 0.266, 0.278, 0.268, 0.276, 0.265, 0.280. (Lead II) 0.263, 0.279, 0.259, 0.280, 0.262, 0.275, 0.264, 0.278, 0.261, 0.280, 0.261, 0.262, 0.278, 0.265, 0.279.

Case 10.—The patient was a 46-year-old American Indian. For six months he had suffered from shortness of breath upon moderate exertion, and attacks of tachycardia which he could stop by breathing deeply. Examination showed that he had *tabes dorsalis*, but no abnormality of the heart was detected. While he was under treatment, several attacks of tachycardia were observed; they were stopped by deep breathing. During normal rhythm there was marked sinus arrhythmia. Electrocardiograms showed that the tachycardia was of supraventricular origin. There was alternation of cycle length, as shown by the following measurements, in seconds: (Lead I) 0.383, 0.363, 0.387, 0.377, 0.399, 0.382, 0.397, 0.377, 0.397, 0.382, 0.388. (Lead III) 0.450, 0.453, 0.462, 0.456, 0.458, 0.442, 0.453, 0.450, 0.460, 0.456, 0.460.

In these cases the alternation in cycle length was apparent to the unaided eye. Measurements were made on the comparator only when inspection revealed the type of irregularity under consideration. It is possible that accurate measurements of other curves would disclose additional examples in which the alternation was less pronounced. Measurements in twenty unselected cases, eight reported by Feil and Gilder,¹ and twelve by Mackinnon,⁵ disclosed this phenomenon in only two (Feil and Gilder). In one of these and in the case reported by Strong and Levine,³ the variations in cycle length were so slight that they could scarcely be detected without accurate measurements. In none of our cases was the alternation of cycle length detected on physical examination.

In none of our cases, with the single exception of Case 7, and in none of those found in the literature, was the alternation of cycle length accompanied by any perceptible alternation or variation in the form or amplitude of the auricular deflections. Alternation in the form or amplitude of the ventricular deflections was somewhat more common.

DISCUSSION

It is possible to account for alternation of the cycle length in auricular paroxysmal tachycardia in a variety of different ways, but in the last analysis it must depend either upon (1) alternation of the interval elapsing between the liberation of successive impulses, or upon (2) alternation in the path or rate of impulse conduction. As to the first possibility, little can be said. The mechanism by which normal cardiac impulses are elaborated is not well understood, and it seems possible, if not probable, that in paroxysmal tachycardia impulses are formed abruptly by an entirely different process. Nevertheless, we know of no

published examples of alternation in cycle length which have been clearly shown to depend solely upon the discharge of impulses by a single center. Cases of bigeminy in which the paired beats are of normal outline, and identical, or nearly so, as regards the form of their component deflections, are not rare, but in such cases it seems probable that successive impulses are not alike in origin. They may be formed either by different centers or by different processes.

We are, on the other hand, familiar with forms of alternation dependent upon variations in the refractory period, absolute or relative, which force successive impulses to pursue different paths or modify the time of their conduction along the same path. Cases in which normal conduction through one of the main bundle branches alternates with block in the same branch, i. e., so-called partial bundle branch block, may be cited as an example of this phenomenon. If auricular paroxysmal tachycardia is caused by the activity of a parasystolic center, surrounded by a zone in which conductivity is depressed, alternation of the cycle length in this disorder may well be the result of a mechanism of the same kind. We may assume in this case that successive impulses pass from the parasystolic center to the main body of the auricular muscle by different routes, or that they travel the same route but require different times.

There is, however, what appears to us a more attractive hypothesis. Alternation of the auricular cycle length was observed by one of us⁷ in a case of auricular flutter in which the auricular rate was 368 (cycle length about 0.163 second). The cycle length shortened, and alternation appeared, when the vagus was strongly stimulated by pressure upon the eye balls. The alternation was accompanied by a slight variation in the form of the circus deflections in the electrocardiogram. It was suggested that both of these phenomena were dependent on the same cause, namely, the presence in the main path of the circus wave of muscle which could not recover completely in the interval between successive circuits of the impulse. The circulating excitation wave was consequently forced to alternate between the shorter circular path in which this muscle lay and a slightly longer path which passed around it. A similar explanation may be offered for the occurrence of alternation in cycle length in auricular paroxysmal tachycardia if we assume that this disorder also is caused by circus rhythm. Uniformity in the contour of the auricular deflections when the length of the auricular cycle alternates requires that the longer and shorter paths be close together throughout their courses, or, at least, in that part which lies in auricular muscle which makes a major contribution to the P deflection. The variation in cycle length, however, is often considerable; it is frequently 0.05 second, and sometimes nearly 0.10 second. This suggests that the two paths must differ considerably in length. The absence of alternation in the form of the auricular deflections when

the alternation of cycle length is pronounced may be accounted for if we suppose that, as has been suggested previously,^{8,9} auricular paroxysmal tachycardia is caused by circus rhythm which involves either the sinoauricular or the atrioventricular node. There is evidence that the tissues of both of these nodes have a relatively long refractory period, and that conduction, in the latter at least, is comparatively slow. Thus a relatively slight alteration in the length of the path through one of the nodes could cause a considerable change in the duration of the cycle without modifying the form of the auricular deflection.

The occasional disturbance of the regular alternation of cycle length is explained by a slight change in the refractory period at times, permitting or causing the circus wave to take a slightly shorter or longer course, as the case may be. In the exceptional case in which there was alternation in the form of the auricular deflection, we may assume that the course of the circus wave was altered in the auricular muscle rather than in the node.

In a separate communication⁹ it was pointed out that many of the features of auricular paroxysmal tachycardia can be explained by circus rhythm involving one of the nodes. Other features of auricular paroxysmal tachycardia have not yet been explained on this basis. Our observations on alternation of the cycle length in this condition were made with the purpose of collecting further evidence bearing on this problem. Although they may be explained in various ways, they seem to us consistent with, and to that extent to support, the view that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized auricular nodes. It is our intention to summarize in a subsequent communication the available evidence bearing on the mechanism of this disorder.

SUMMARY

1. Close inspection of the electrocardiograms in one hundred unselected cases of auricular paroxysmal tachycardia revealed ten cases in which there was a slight irregularity characterized by alternation in the lengths of the cycles.

2. This phenomenon may be explained in various ways, depending upon one's views as to the nature of the underlying mechanism in this disorder.

3. Our observations are consistent with, and to that extent support, the view that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized auricular nodes.

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CAPILLARY BLOOD PRESSURE IN MAN. DIRECT MEASUREMENTS IN THE DIGITS OF PATIENTS WITH RAYNAUD'S DISEASE AND SCLERODERMA BEFORE AND AFTER SYMPATHECTOMY

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BY MEANS of the direct microinjection method, Landis¹ measured the capillary blood pressure in the digits of three patients with Raynaud's disease during typical spastic and subsequent hyperemic stages. Previous studies^{2, 3, 4} with the direct method demonstrated that a variety of factors induced changes in the digital capillary blood pressure which were qualitatively similar in both normal capillaries and the abnormally large capillaries of Raynaud's disease and scleroderma. These factors were neurogenic vasoconstrictor stimuli, epinephrine intravenously, reactive hyperemia, and elevation of arterial pressure produced by paredrinol sulfate.

The present communication reports additional observations on the digital capillary blood pressure of patients with Raynaud's disease and scleroderma both before and after interruption of the sympathetic innervation to the digits.

METHODS

General.—The capillary blood pressure was measured in the nail folds of the fingers by the direct microinjection method.^{7, 8} The general methods, conditions, and precautions were similar to those described in detail in a previous communication under the category, *general*.² Except for measurements which were made during vasospastic circulatory arrest, capillary blood pressure was measured *only* when the blood flow in the capillary remained visibly unaltered from the normal.

Particular.—Of the eleven patients who were studied, seven were women and four were men. Nine of the patients had Raynaud's disease. In six of these there were associated sclerodermatous changes in the fingers. The other two patients had scleroderma alone. The arterial pressure was normal in eight of the patients, below 100 mm. Hg, systolic, in two, and above normal during the first measurement on the remaining subject.

The ready occurrence of vascular spasm, with circulatory arrest in the digits, almost always necessitated warming the body in order to obtain "moderate digital vasodilatation" (digital skin temperature between 30° C. and 33° C.). Such temperatures were not invariably attained, and comparable states of digital circulation from patient to patient could not always be obtained. Circulatory arrest in the nail folds was induced by exposing the fingers to room temperatures below 20° C. (usually 15° C. to 17° C.) and omitting the heating of the body. Local increases of venous pressure in the digits were produced by inflating a pneumatic cuff encircling the upper arm to pressures below diastolic arterial pressure.⁸

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Interruption of the sympathetic innervation to the digits was accomplished (1) temporarily, by injecting a 2 per cent procaine solution into the region of the stellate and upper thoracic sympathetic ganglia, and (2) permanently, by preganglionic sympathectomy. Preganglionic sympathectomy of the upper extremity, according to the method of Smithwick,⁹ was achieved in three patients (F. G., C. M., and B. B.).

Capillary blood pressures represented by a single value indicate the average pressure in one capillary, and were obtained by averaging the individual values of a series of readings made during a single continuous observation on that capillary.

RESULTS

Not infrequently there was flushing of the nail folds in which capillary blood pressure was being measured, while the remainder of that finger and the other fingers remained grayish or purplish blue. This erythema was attributed to a disturbance of the local circulation in the minute vessels, caused, perhaps, by local liberation of H substance by the trauma of piercing the nail fold with the micropipette.

DIGITAL INNERVATION INTACT

Capillary Blood Pressure During Vasospastic Circulatory Arrest in the Digits.—During vasospastic circulatory arrest induced in the fingers by cold, the capillaries of the nail fold lost their pink color and smooth outlines. They became widely dilated loops of indented, irregular contour, filled with a stationary mass of dark, bluish-red blood. Apparently because of the loss of its fluid element, the blood became more compact and more viscid. This was indicated by the less free movement of erythrocytes into and out of the tip of the micropipette, by the frequent need of negative pressure to draw blood into the micropipette, and by the adherence of clumps of erythrocytes to the micropipette when it was withdrawn from the capillary.

In order to obtain accurate measurements, the compact mass of erythrocytes was first broken into a loose, freely moving suspension. This was accomplished by injecting a small amount of solution from the micropipette into the capillary. Fluid thus introduced was seen to drain quickly through the venous limb of the capillary and carry with it some of the compact erythrocyte mass, leaving behind a more loose suspension.

During vasospastic circulatory arrest, the digital capillary blood pressure in all portions of nine capillaries of three subjects varied between 7.0 mm. Hg and 12.5 mm. Hg (average, 9.7 mm. Hg) (Table I, Fig. 3 open circles).

When the digital circulation was normal, raising the venous pressure in the upper extremity caused the capillary blood pressure to rise promptly, and, within one to two minutes, to exceed the venous pressure.⁸ During vasospastic circulatory arrest, a similar increase in the venous pressure induced a much slower rise in the capillary blood pressure. Five to seven minutes were required to attain maximum values. These

TABLE I
CAPILLARY BLOOD PRESSURE DURING CIRCULATORY ARREST INDUCED BY COLD, AND DURING SUBSEQUENT REFLEX VASODILATATION

SUBJECT, SEX, AGE	CHARACTER OF CAPILLARY LOOPS	LOCATION IN CAPILLARY WHERE BLOOD PRESSURE WAS MEASURED	CIRCULATORY ARREST			REFLEX VASODILATATION		
			SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. Hg	CAPILLARY BLOOD PRESSURE MM. Hg	SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. Hg	CAPILLARY BLOOD PRESSURE MM. Hg
A. L. (M, 27)	Large dilated	Summit	14.9	104/64	84			
		Summit	14.9	104/64	84			
		Summit	14.9	104/64	84			
M. L. (F, 48)	Large dilated	{Summit	14.6	110/72	91	22.2	104/74	40
		{Venous limb	14.6	110/72	91			
F. G. (M, 31)	Large dilated	Venous limb	16.2	104/66	85			
		Venous limb	14.6	122/74	98	20.5	122/74	24
		Venous limb	20.9†	122/74	98	20.3	122/74	23.5 to 34.5
		{Venous limb	16.2	104/66	85			
		{Arteriolar limb	16.2	104/66	85			
		{Arteriolar limb	14.6	122/74	98			
		Summit	16.4	104/66	85			

†Very slow flow through capillary persisted.

Two sets of observations made on a single capillary are indicated by brackets.

approximated, but failed by 2 to 3 mm. Hg to equal, the increased venous pressure (Fig. 1). Suddenly lowering the elevated venous pressure to its initial level caused the capillary blood pressure to fall quickly to its original level (Fig. 1). The rapidity of this fall equalled that which occurred when the capillary blood flow was swiftly onward.

Releasing digital vasospasm by producing reflex vasodilatation caused the blood flow to return in the capillaries, and digital capillary blood pressure to increase at times to values above those usually encountered. In three capillaries, maximum values of 24, 34.5, and 40 mm. Hg were obtained (Table I). The digital skin temperature lagged considerably behind the return of capillary blood flow and the rise in capillary blood pressure (Table I).

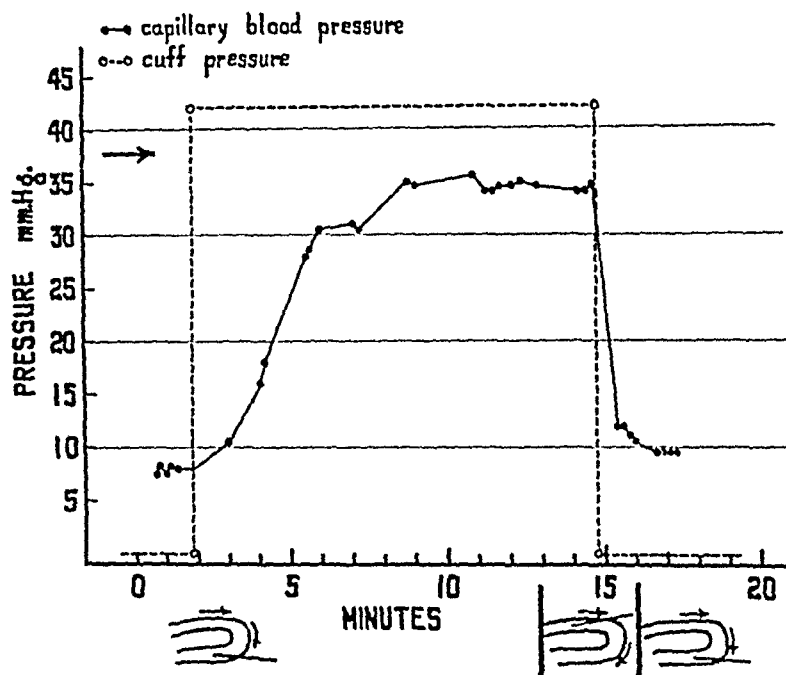


Fig. 1.—Response of the blood pressure in a single digital capillary to increased venous pressure during vasospastic circulatory arrest induced by cold.

The ordinates indicate pressure (mm. Hg) in both the occluding cuff and the capillary; the abscissae, time in minutes. The solid line indicates capillary blood pressure, and the dotted line, pressure in the occluding cuff. The large horizontal arrow indicates venous pressure in the back of the hand when the cuff pressure was 42 mm. Hg. In the diagrams of the capillary, the straight line shows the location of the micropipette in the capillary, and the arrows, the direction of blood flow before circulatory arrest.

When the circulation returned to the capillaries after a period of vasospastic circulatory arrest, stationary erythrocytes were found just beyond the visible summits of a few capillaries. These erythrocytes were not in the visible current of the capillary blood stream, and appeared to be not even connected with the adjacent capillaries. Such erythrocytes were present in either of two forms: (a) as loose aggregations of widely-spaced, stationary, individual cells ("fuzz") (Fig. 2A), and (b) as small, compact, nonmoving masses of packed cells ("button") (Fig. 2B). There is reason to believe that these aggregations

of erythrocytes are not extracapillary, as they appear to be, but are actually intracapillary.

On one occasion, individual erythrocytes were repeatedly thrown off from the visible capillary stream at the junction of the arteriolar limb with the summit. Flung beyond the visible summit, these cells became stationary, and, when joined by others, formed a loose aggregation ("fuzz"). In time, closer clumping occurred, but no compact mass ("button") was formed. Occasionally, a few well-separated, stationary erythrocytes connected a compact clump ("button") with the visible summit of the capillary (Fig. 2C).

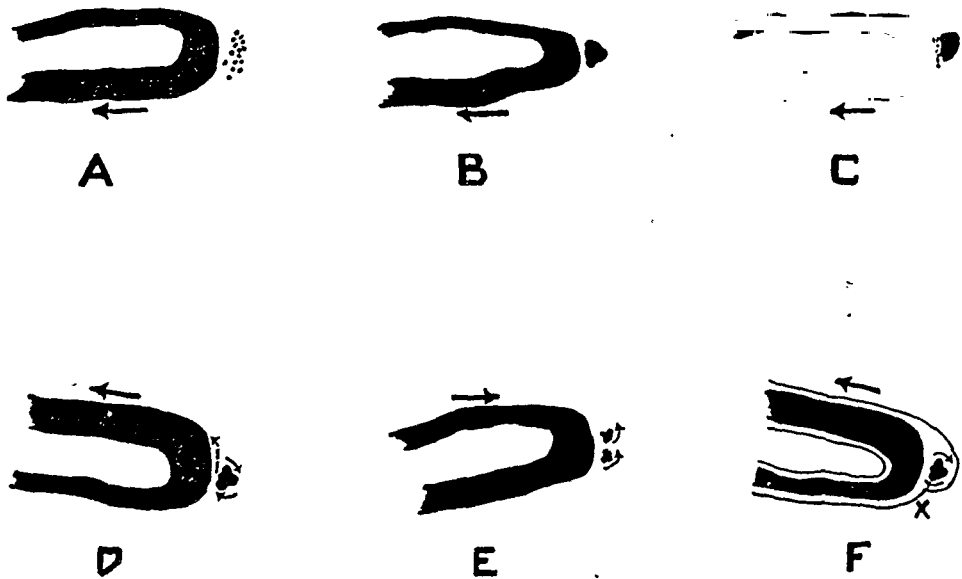


Fig. 2.—Diagram of types of erythrocyte aggregation found outside the visible summit of the capillary when digital circulation returned after a period of standstill.

The capillary is diagramed in black; the large arrows indicate the direction of blood flow, and the small arrows, the direction of rotation of clumps of erythrocytes.

A, Loose aggregation of individual erythrocytes ("fuzz"); B, single, stationary clump of packed erythrocytes ("button"); C, individual cells connecting summit of capillary blood stream with a clump of packed cells; D, single clump of packed erythrocytes in rotation ("pinwheel"). The dotted arrow indicates the path followed by the clump in returning to the main stream; E, two separate clumps of erythrocytes rotating beyond the summit of a single capillary; F, possible mechanism by which erythrocytes remain outside the main capillary stream.

Peripheral to the erythrocyte portion of the capillary blood stream is the clear plasma layer. It is assumed that, at the junction of the arteriolar limb with the summit (point X) there is a localized capillary constriction which deflects the blood flow from the summit.

On several occasions, compact masses of erythrocytes were rotating like "pinwheels" just beyond the visible summit of the capillary (Fig. 2D). These masses were usually of irregular contour, and their rotation always took place in a direction opposite that of the current in the adjacent capillary. Two separate clumps have been found rotating beyond the summit of a single capillary (Fig. 2E). Once a rotating clump of erythrocytes was observed to move slowly toward the venous limb of the capillary, and then suddenly enter the main capillary stream at the junction of the venous limb with the summit (Fig. 2D, dotted arrow). In a similar manner, loose aggregations of erythrocytes ("fuzz") have been seen to enter the adjacent capillary.

Capillary Blood Pressure When Digital Blood Flow Was "Normal."

—The capillary blood pressure in the same location of the same capillary was quite constant (variation, 2 to 3 mm. Hg) throughout any single experiment when the digital skin temperature remained relatively unchanged (Table II), but from person to person, and even from capillary to capillary in the same subject, the capillary blood pressure varied considerably, even though the digital skin temperature was brought to the same level (Fig. 3). These variations were usually less marked than those previously observed in normal and hypertensive subjects.³

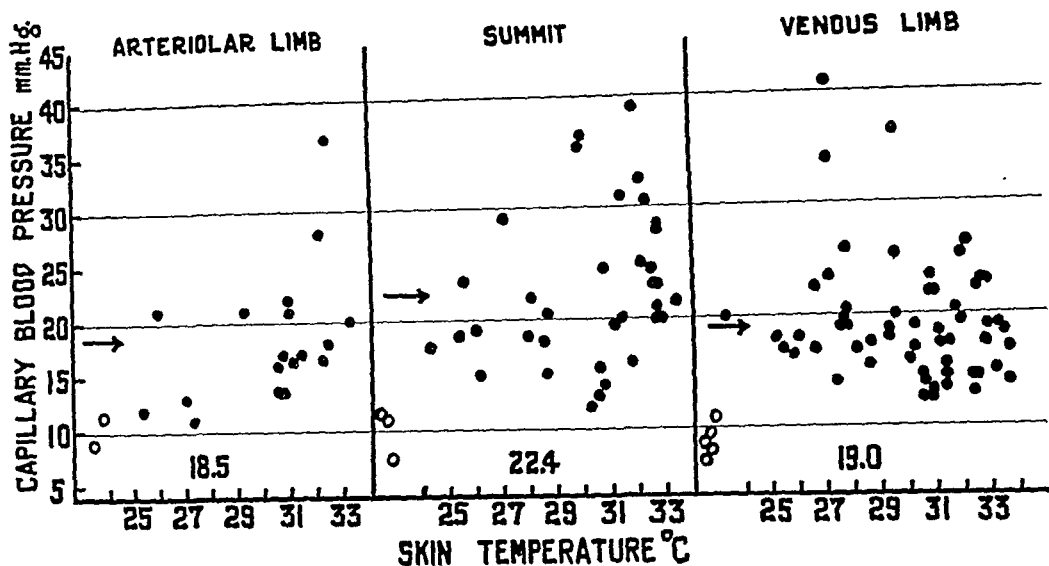


Fig. 3.—Digital capillary blood pressure in different locations in the capillary at varying digital skin temperatures. Digital innervation intact.

Pressures, represented by open circles, were obtained during vasospastic circulatory arrest (skin temperatures about 15° C.) and all others during active blood flow.

Figs. 3, 4, 5 are similarly constructed. Ordinates, digital capillary blood pressure in mm. Hg; abscissae, digital skin temperature in degrees Centigrade. Each dot represents the average capillary blood pressure in the designated location of a single capillary at the skin temperature indicated by the abscissa. Each horizontal arrow and number above the abscissa line gives the average of the pressures represented by the corresponding dots.

Skin Temperature.—No measurements of digital capillary blood pressure in the same capillary during large changes in digital skin temperature were obtained. However, the skin temperature was measured at the time of each measurement of capillary blood pressure. This permits evaluation of the relationship between the two (Fig. 3). Over a wide range of temperatures (from 24° C. to 33.5° C.), the digital capillary blood pressure did not change significantly with the skin temperature (Fig. 3). Excluding values obtained during circulatory arrest, the capillary blood pressure and its range of variation were similar at all levels of skin temperature. Only in the summit of the capillary at the higher temperatures (31° C. to 33° C.) was there a tendency toward higher values. This was regarded as inconclusive.

Gradient of Fall of Pressure Through the Capillary.—The average digital capillary blood pressure in eighteen arteriolar limbs was 18.5 mm.

TABLE II

SUCCESSIVE MEASUREMENTS OF CAPILLARY BLOOD PRESSURE IN THE SAME LOCATION IN A SINGLE CAPILLARY DURING ONE OBSERVATION PERIOD

SUBJECT, SEX, AGE	CHARACTER OF CAPILLARY LOOPS	LOCATION IN CAPILLARY WHERE BLOOD PRESSURE WAS MEASURED	FIRST MEASUREMENT			SECOND MEASUREMENT			DIFFER- ENCE MM. HG.	
			SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG READING "MEAN"	CAPILLARY BLOOD PRESSURE MM. HG	SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG READING "MEAN"	CAPILLARY BLOOD PRESSURE MM. HG		
<i>A. Innervation Intact</i>										
T. A. (M, 26)	Large dilated	Arteriolar limb	30.9	90/56	73	30.9	96/56	76	22	1.0
F. H. (M, 38)	Moderately large	Venous limb	30.7	118/62	90	30.7	118/62	90	22	0.0
M. S. (F, 19)	Large dilated	Venous limb	29.2	86/50	68	30.0	94/60	77	16	2.0
C. M. (F, 29)	Large dilated	Venous limb	27.0	128/86	107	27.0	128/86	107	41	7.0
		Summit	27.0	128/86	107	26.1	128/86	107	15	14
		Summit	32.7	120/78	99	32.3	120/78	99	30.5	2.5
F. G. (M, 31)	Large dilated	Summit	33.4	118/78	98	32.7	124/84	104	23	1.5
		Venous limb	33.4	118/78	98	32.3	125/86	106	19.5	1.0
		Venous limb	30.1	130/82	106	27.5	116/78	97	19	0.0
M. L. (F, 48)		Venous limb	29.2	130/82	106	27.5	116/78	97	19.5	1.0
	Large dilated	Venous limb	29.0	?		31.0	108/62	85	21	3.0
	Quite normal	Summit	25.3	110/76	93	27.9	122/86	104	18.5	0.0
<i>B. Sympathetic Innervation Interrupted</i>										
B. B. (F, 44)	Quite normal	Summit	29.4	106/76	91	29.4	106/76	91	17	2.5
F. G. (M, 31)	Large dilated	Summit	31.9	110/80	95	34.0	110/80	95	17.5	0.5
		Venous limb	32.8	116/76	96	31.2	128/88	108	23	5.5
C. M. (F, 29)	Large dilated	Venous limb	32.4	126/86	106	33.8	122/82	102	26	3.5

Hg (range, 11 to 36.5 mm. Hg); in thirty-one summits, 22.4 mm. Hg (range, 12 to 39 mm. Hg); and in fifty-two venous limbs, 19 mm. Hg (range, 12.5 to 41 mm. Hg) (Fig. 3). Hence, the gradient of fall of pressure in these dilated capillaries was small, namely, 2 to 3 mm. Hg.

Even more significant was the absence of a gradient of more than a few millimeters of mercury between the various locations of the *same* capillary when measurements were made in a single experiment during which digital skin temperature and brachial arterial pressure remained constant (Table III).

It is emphasized that the majority of these measurements, both in the same and in different capillaries, were made when there was "moderate vasodilatation" (skin temperature, $30^{\circ}+C.$), and blood flowed swiftly and continuously onward through the capillaries.

SYMPATHETIC INNERVATION OF THE DIGITS INTERRUPTED

In some cases, preganglionic sympathectomy of the upper extremity was followed by a return toward normal in the morphology of the capillaries. The abnormally large loops, with slowly flowing, bluish-red blood, became smaller, narrower loops containing rapidly flowing, pink blood. This change was attributed, not to the removal of the sympathetic innervation per se, but to the improvement in digital circulation which followed the abolition of periods of circulatory arrest. A similar change was noted in one case after one month's hospitalization in a warm environment. During this period, vasospastic periods spontaneously became much less frequent and less prolonged.

Even after removal of sympathetic activity by satisfactory preganglionic sympathectomy, the digital capillary blood pressure still varied considerably from subject to subject (Fig. 4), and even from capillary to capillary in the same subject during a single experiment.

Skin Temperature.—After sympathectomy, the digital skin temperatures were higher, ranging between $30^{\circ}C.$ and $35^{\circ}C.$ At all skin temperatures throughout this range, the capillary blood pressures for all locations in the capillary fell within the same limits. There was no relationship between capillary pressure and digital skin temperature (Fig. 4).

When the digital skin temperature remained relatively constant (variation less than $2^{\circ}C.$), repeated measurements of the capillary blood pressure in the same location of the same capillary varied but slightly (5.5 mm. Hg) (Table II).

Gradient of Fall of Pressure Through the Capillary.—The average digital capillary blood pressure in eleven arteriolar limbs was 27.8 mm. Hg (range, 19.5 to 36 mm. Hg); in twenty-four summits, 25.2 mm. Hg (range, 14 to 40 mm. Hg); and in twenty-four venous limbs, 21.6

TABLE III
CAPILLARY BLOOD PRESSURE IN DIFFERENT LOCATIONS IN THE SAME CAPILLARY.
DIGITAL SKIN TEMPERATURE AND BRACHIAL ARTERIAL PRESSURE CONSTANT

SUBJECT, SEX, AGE	CHARACTER OF CAPILLARY LOOP	SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG		CAPILLARY BLOOD PRESSURE MM. HG				GRADIENT
			READING	"MEAN"	ARTERIO- LAR LIMB	SUMMIT	VENOUS LIMB	VENULE	

<i>A. Innervation Intact</i>									
F. H. (M, 38)	Moderately large	30.7	118/62	90		24.5	22		+2.5
B. B. (F, 44)	Quite normal	25.3	110/76	93		18.5	17		+1.5
T. A. (M, 26)	Large dilated	30.9	96/56	76	22			15	+7.0
	Large dilated	31.1	90/56	73	16.5		17.5		-1.0
F. G. (M, 31)	Large dilated	30.7	126/80	103	17		23.5		-6.5
		32.7	124/84	104		20	23		-3
		32.7	116/80	98		23	17.5		+5.5
		30.5	104/66	85	13.5	13	12.5		+0.5, +0.5
		30.5	104/66	85	16	15.5	14.5		+0.5, +1.0
E. B. (F, 44)	Large and normal	25.9	170/116	143	21	19	18		+2, +1

<i>B. Sympathetic Innervation Interrupted</i>									
C. M. (F, 29)	Large dilated	30.7	114/82	98	36	27			+9.0
F. G. (M, 31)	Large dilated	31.9	110/80	95	27	18			+9.0
		31.4	122/86	104	26		32.5		-6.5
B. B. (F, 44)	Quite normal	30.5	106/78	92	32.5		16		+16.5
		30.4	110/76	91	21	20			+1.0
		30.3	110/76	93	34	36			-2.0
		29.4	106/76	91		19.5	13.5		+6.0
F. H. (M, 38)	Moderately large	29.0	122/70	96		35.5	32.5		+3.0

mm. Hg (range, 13.5 to 40 mm. Hg). The gradient of fall of pressure through these capillaries was, therefore, relatively small, and more apparent in the average values than in the scatter chart of all measurements (Fig. 4). A moderate gradient through the capillary was present when the digital capillary blood pressure was measured in different locations of the same capillary during a single experiment throughout which skin temperature remained constant (Table III).

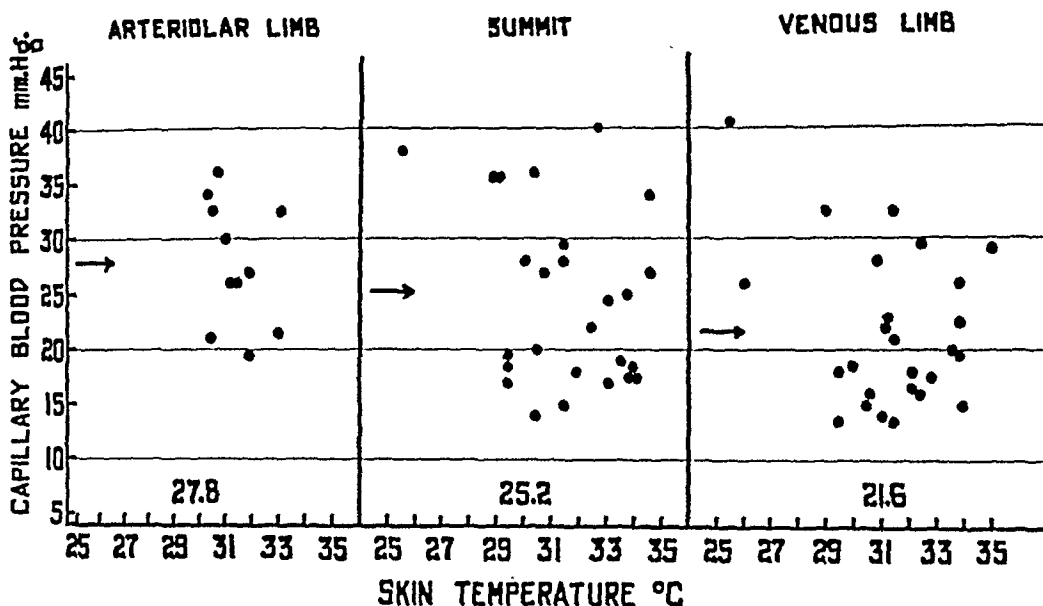


Fig. 4.—Digital capillary blood pressure in different locations in the capillary at varying digital skin temperatures. Sympathetic innervation interrupted. Gradient of fall of pressure through the capillary is greater than during intact innervation, but is still small.

COMPARISON OF CAPILLARY BLOOD PRESSURE WHEN THE INNERVATION WAS INTACT WITH THAT AFTER INTERRUPTION OF SYMPATHETIC ACTIVITY

Although the average capillary blood pressure for each location in the capillary was somewhat higher after interruption of sympathetic activity than before interruption (Fig. 5), this was striking for only the pressures in the arteriolar limb. In this location the average pressure was 9.3 mm. Hg higher after sympathectomy than before, and the individual values scattered over a higher range. In the summit and venous limb the individual values scattered over the same limits after sympathectomy as before, and the differences in the average values were but 2.8 mm. Hg for the summit and 2.6 mm. Hg for the venous limb. The gradient of fall of pressure in the capillary seemed more definite after interruption of sympathetic activity than before (Table III, Fig. 4).

In only one case was the capillary blood pressure measured in the same location of the same capillary (two venous limbs) both before and after sympathectomy. In one venous limb the pressure before sympathectomy was 15 to 19 mm. Hg, and after sympathectomy, 19.5 mm. Hg; in the

other venous limb, before sympathectomy, it was 13.5 to 18.5 mm. Hg. and, after sympathectomy, 22.5 mm. Hg.

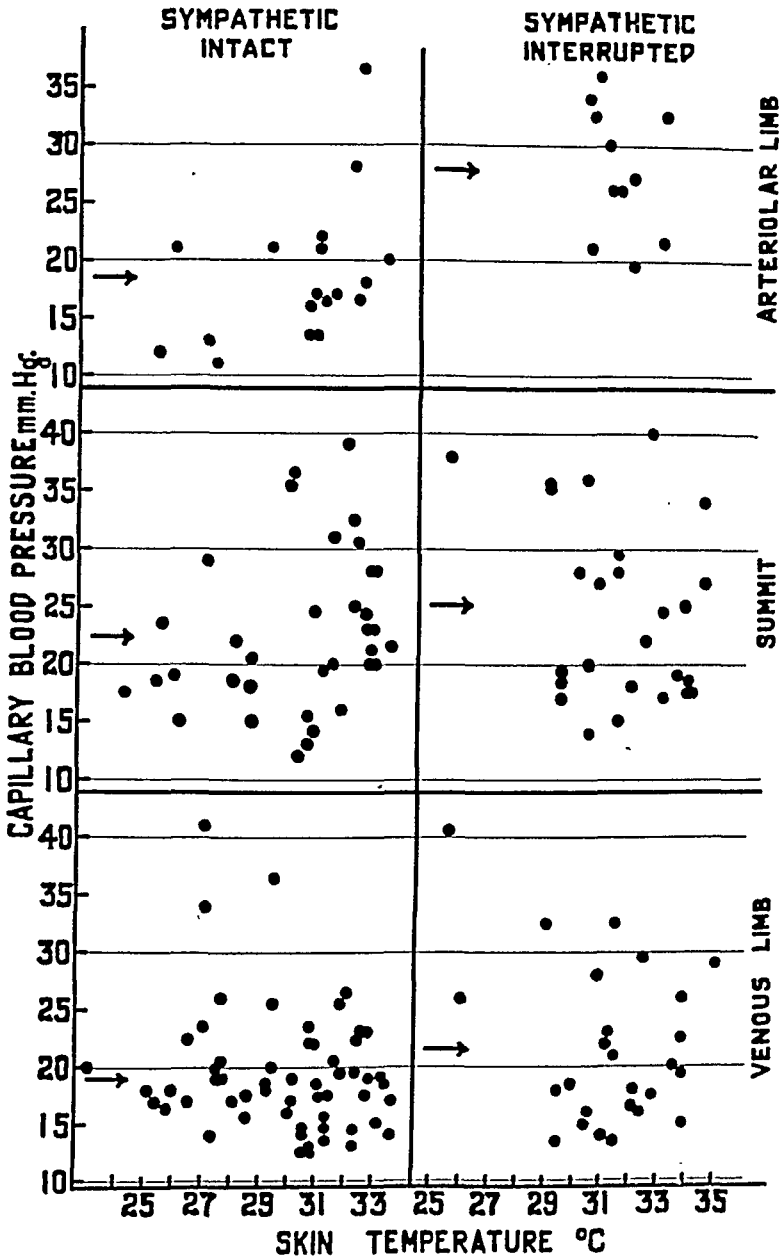


Fig. 5.—Digital capillary blood pressure in different locations in the capillary when innervation was intact, compared with similar pressures obtained after interruption of sympathetic innervation.

DISCUSSION

The digital capillary blood pressures of 7.0 to 12.5 mm. Hg during vasospastic circulatory arrest and 24 to 40 mm. Hg during subsequently induced reflex vasodilatation agree favorably with the values obtained by Landis¹ under similar conditions. Our data also confirm the observations and conclusions of Landis¹ that vasospastic circulatory arrest in the digits is precapillary in origin, and that it is associated with patency

of the capillaries and venous channels. The following observations, made during circulatory arrest in the capillary, substantiate this conclusion: (1) When fluid is injected into the capillary it drains readily out of the venous limb; (2) capillary blood pressure rises slowly during an induced increase in venous pressure in the upper extremity; and (3) capillary blood pressure falls promptly when the increased venous pressure is quickly reduced.

Several factors may explain why erythrocytes are found beyond the visible capillary blood stream when digital circulation returns after a period of arrest: (1) The assumption that capillaries possess independent, localized contractility,¹⁰ and (2) the fact that blood flows through the capillary in an axial stream, the central erythrocyte portion of which is visible, and the peripheral plasma layer, invisible.

Localized constriction of the capillary at the junction of the arteriolar limb with the summit (point *x*, Fig. 2*F*) would produce an indentation at this point. This protrusion would deflect the blood stream and prevent it from sweeping into the outermost summit of the capillary, where now a stagnant "pool" is formed. Such a localized constriction during vasospastic circulatory arrest, if it persisted after the return of blood flow in the capillary, could trap a compact clump of cells ("button") in the "pool" at the summit. The clear plasma layer between the clump of cells and the visible erythrocyte portion of the axial stream gives the illusion that the clump is outside the capillary. When the plasma layer of the capillary stream impinges on the excrescences of the clump of cells, the entire mass is set into rotation like a "pinwheel"; otherwise, the mass remains stationary. As the capillary stream sweeps past the indentation, it may fling off individual erythrocytes into the "pool" at the summit, where they accumulate in loose aggregations ("fuzz"). Relaxation of the local constriction would permit the capillary stream to sweep into the "pool" at the summit and carry away in itself everything therein contained.

The anoxemia of circulatory arrest may so damage the capillary endothelium that it becomes sticky, causing erythrocytes to adhere to it. This may also be a factor in holding stationary individual or clumped erythrocytes against the force of the peripheral layer of the capillary blood stream.

A widely accepted view holds that the gradient of pressure from the arteriolar to the venous limb of the capillary is of considerable magnitude (20 mm. Hg). It is, therefore, significant that in the abnormally large capillaries of these patients the gradient of pressure between the arteriolar and venous limbs was small (2 to 3 mm. Hg). This was maintained even during the swift blood flow associated with "moderate digital vasodilatation." In these capillaries a small gradient of pressure is sufficient to produce a swift flow of blood, and factors other than capillary blood pressure and blood osmotic pressure influence the passage of fluid through the capillary membrane.

In abnormally large capillaries, just as in those of normal size, wide variations in digital skin temperature (24°C. to 34°C.) were not accompanied by significant changes in digital capillary blood pressure. Only when the digital circulation slowed markedly, or stopped completely, did the capillary blood pressure fall outside the usual range. In these abnormally large capillaries there also appears to be a homeostatic mechanism³ which permits wide fluctuations in digital blood flow without great change in digital capillary blood pressure.

When compared at similar digital skin temperatures, the capillary blood pressure after loss of sympathetic activity was not strikingly different from that before sympathectomy (Fig. 5). In the summits and venous limbs no significant differences were evident. The somewhat greater capillary blood pressures in the arteriolar limb after sympathectomy suggest a release, at least to some extent, of arteriolar tonus.

SUMMARY

1. During vasospastic circulatory arrest, induced in the fingers by cold, (a) digital capillary blood pressure varied between 7.0 and 12.5 mm. Hg (average, 9.7 mm. Hg); (b) digital capillary blood pressure *rose slowly* in response to induced increases in venous pressure, but *fell promptly* when the increased venous pressure was suddenly lowered; (c) cessation of blood flow through the capillaries was caused by closure of vessels proximal to them. The capillaries, venules, and veins remained patent.

2. Erythrocytes in clumps or loose aggregations may be isolated outside the central capillary blood stream when the digital circulation returns after a period of vasospastic circulatory arrest. Localized constriction of the capillary, or stickiness of the capillary endothelium, or both, may account for this.

3. In fingers with intact innervation the average digital capillary blood pressure was as follows: arteriolar limb, 18.5 mm. Hg; summit, 22.4 mm. Hg; and venous limb, 19 mm. Hg. The gradient of fall of pressure through the capillary was small, usually less than 3 mm. Hg.

4. In fingers deprived of sympathetic innervation the average digital capillary blood pressure was as follows: arteriolar limb, 27.8 mm. Hg; summit, 25.2 mm. Hg; and venous limb, 21.6 mm. Hg. The somewhat greater capillary pressure in the arteriolar limb suggests release of arteriolar tone. The gradient of pressure in the capillary is still small (6 to 7 mm. Hg).

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Clinical Reports

ANEURYSM OF THE ABDOMINAL AORTA, WITH RUPTURE INTO THE DUODENUM

CASE REPORT AND REVIEW OF THE LITERATURE

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THE purpose of this paper is to present a case of abdominal aneurysm which ruptured into the duodenum, and to review thirty-one similar cases from the literature. Although the first of these was found in 1843,² the phenomenon must have been observed prior to that time, for Chamel and Dalmas,¹ in 1833, stated that "rupture into the gastrointestinal tract is one of the complications of abdominal aneurysm."

Table I gives the essential data in each of the thirty-one cases.²⁻³¹ There were twenty-five males and five females (in one case the sex was not given). The patients' ages varied from 20 to 81 years. Between these extremes, the distribution of cases is fairly even.

The usual manifestations were abdominal pain, an abdominal mass, hematemesis, melena, and shock. The combination of these symptoms and their rapidity of development varied from case to case. Bernacchi's¹⁰ patient had been cognizant of an enlarging abdominal mass for many years; during convalescence from pneumonia, after days of abdominal pain, he was awakened from sleep by hematemesis, which was followed rapidly by death. In a second case the patient was aware of an abdominal mass for two years before hematemesis occurred and death ensued. Other patients gave histories of gradually progressing weakness, with subsequent hemorrhages from the gastrointestinal tract. In still others, prodromal symptoms were present in the form of pain in the epigastrium, lumbar area, umbilical region, or in the loin. In some instances these symptoms were present as long as two years before the aneurysm ruptured. Particularly puzzling was a patient with symptoms of peptic ulcer for many years; suddenly, severe pains developed and hematemesis followed.

The time relationship of death to the onset of hematemesis varied. It was almost immediate in some cases, and, in others, was as long as six weeks. In the interim, one or many recurrences of melena and bloody vomiting occurred.

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The most important physical sign was a palpable abdominal mass, usually above the umbilicus and to the left of the midline. Pulsation was present, as a rule, but was rarely expansile in nature. In some cases a thrill was felt and a murmur heard.

Pathologic Observations.—Most of the aneurysms were of the saccular type; others were so-called aneurysmal dilatations. Their location in relation to the branches of the abdominal aorta was given in only a few instances. One aneurysm was close to the diaphragm, and the others were found at all levels from above the celiac axis to just above the bifurcation of the aorta. In regard to organs perforated by the aneurysms, five ruptured into the stomach,^{9, 15, 27, 29, 32} one into the jejunum,¹⁵ one into the small intestine⁴ (the exact site was not specified), and twenty-four into the duodenum (twenty-three into the third part, one into the second part).

CASE REPORT

A white man, aged 53, entered St. Vincent's Hospital, New York City, Aug. 29, 1935, complaining of painful "arthritis" of the right hip. In May, 1935, he had had Type I pneumococcus pneumonia, complicated by empyema, and later by arthritis. On admission it was noted that the limb in question was shortened slightly, and was rigid because of pain. Roentgenologic study disclosed destruction of the articular cartilages and narrowing of the joint space. For the remaining three months of his life the patient was bedridden. During the first half of this period he seemed more or less comfortable, after which he began to complain of constant pain in the epigastrium. At first the only abnormality was tenderness and spasm of the rectus muscles. Later, a pulsating mass became palpable in the epigastric region. The mass increased in size until it reached that of a small orange. A bruit was heard over it. Two days before death the patient had sudden hematemesis; this recurred several times, and was followed by melena up to the time of death. The blood Kahn reaction was negative. Roentgenologic study of the stomach showed a deformity suggesting extrinsic pressure. The gastric contents and urine were normal. Throughout the course there was a fever of 99.6° F., with an occasional rise to 100° F. One blood cell count a month before death showed 12,400 leucocytes, 67 per cent polymorphonuclear leucocytes, 28 per cent lymphocytes, four monocytes, and one eosinophil.

Autopsy.—The important lesions were in the abdominal aorta and duodenum. On the anterior surface of the aorta, 2½ cm. below the renal arteries, there was a saccular aneurysm which measured 7½ × 7 × 4 cm. Its external surface was firmly adherent to the outer surface of the third portion of the duodenum. The adhesion was thick and fibrous, and could not be separated without tearing both structures. On opening the aorta it was found that the aneurysm was filled with a firm thrombus, and that it communicated with the lumen of the aorta through an opening 4 cm. in diameter (Fig. 1).

The rest of the aorta was not dilated and was elastic. Just above the aortic valves, and in the arch, small flecks of atheroma were observed. Scattered through the descending thoracic and abdominal portions were raised yellow plaques. No gross changes suggestive of syphilis were observed except around the upper rim of the aneurysm, where the intima was wrinkled, raised, and pearly grey.

On opening the gastrointestinal tract an irregular perforation was found in the posterior wall of the mid-transverse limb of the duodenum; this opening communicated with the underlying, adherent aneurysm (Fig. 2). A thin strand of



Fig. 1.—Abdominal aorta opened posteriorly, exposing mouth of aneurysm. Aneurysm itself is filled with thrombus. Defects at margins (c) are caused by removal of blocks of tissue. *a* indicates mouth of celiac axis. *b* indicates mouth of superior mesenteric artery.



Fig. 2.—Third portion of the duodenum. Note the irregular ulcer. A small band of mucosa extends from one margin to the other.

duodenal mucosa extended across the perforation. The margins of the perforated area were sharp, and showed nothing indicative of a pre-existing peptic ulcer. Clotted and free blood was found in the stomach and in the small and large intestine.

The heart weighted 350 Gm. and appeared to be well preserved.

Anatomic Diagnosis.—Saccular aneurysm of the anterior wall of the abdominal aorta, with rupture into the third portion of the duodenum; massive hemorrhage into the gastrointestinal tract; ischemia of the liver and kidney; mild atherosclerosis of the aorta; mild atherosclerosis of the cerebral vessels.

Microscopic Study of the Aorta.—All of the ascending aorta was cut into serial blocks in such a manner as to include its entire circumference. Many sections were prepared from the descending aorta, especially through the aneurysm. The stains employed were hematoxylin and eosin, Weigert's elastic tissue stain, the Masson-Goldner trichrome stain, and the Giemsa and Gram stain for bacteria.

Only minor changes were observed in the ascending aorta, such as atherosclerosis with focal compression atrophy of the underlying media, occasional zones of medial degeneration of the "muscle loss" type, and a sprinkling of fine granules of calcium. Nothing more significant was found elsewhere until sections through the aneurysm were studied. Since all of its layers exhibited alterations, it might be well to consider each tunica separately, and describe the changes as they were seen from just above to just below the sac.

The intima above, around, and below the aneurysm was densely fibrous. At the margins the same sclerotic thickening was observed, together with several atherosclerotic plaques. In the adjacent aneurysmal wall some of these were ulcerated and covered by thrombus.

The media presented a varying appearance. That immediately superior to the aneurysm contained endothelial-lined channels of wide caliber, lymphocytes, and large round cells. The changes did not resemble those of syphilis. As the media dipped into the aneurysmal sac it split and disappeared, so that in its depth only hyalinized fibrous tissue made up the wall.

The elastic media of the inferior wall of the aneurysm was compressed into a narrow layer devoid of muscle cells. Just below the sac the elastic lamellae were reduced in numbers and were thin and fragmented. The adventitia over the entire aneurysm was thick and fibrotic. Portions of adjoining structures, such as the duodenum and the inferior vena cava, were intimately fused with it. Incorporated in it was the inferior mesenteric artery, which was thick walled and thrombosed. The thrombus was completely organized. Scattered through the adventitia were numerous lymphocytes and large collections of macrophages filled with hemosiderin. In several fields there were dense collections of polymorphonuclear leucocytes, forming abscesses $\frac{1}{2}$ mm. in diameter. In one of the abscesses there were many large, Gram-positive bacilli which resembled *B. subtilis* morphologically. The organisms were also seen on the lumen surface of the thrombus which filled the aneurysm. The thrombus itself, at its junction with the surface of the aorta, showed fibroblastic proliferation.

Section of other organs disclosed arteriosclerosis of the pulmonary vessels, anthracosis of the lung, mild granular degeneration of the liver cells, ischemia of the spleen, arteriosclerosis of the small renal arteries, and mild atrophy of the testicular tubules. The pancreas, thyroid, adrenal, pituitary, and parathyroid were apparently normal. Search for bacteria beyond the aneurysm was fruitless.

This case illustrates one of the rarer sites of rupture of abdominal aneurysms. The cause of the aneurysm can only be surmised. There seems to be no reason to implicate syphilis. The same applies to trauma and tuberculosis. However, atherosclerosis, a common cause of ab-

TABLE I

CLINICAL DATA

	DATE	AUTHOR	AGE	SEX	PERTINENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC CHANGES
1	1843	Salmon ²	59	M	Ill for about 1 month. Weakness and intestinal hemorrhage	Tender, hard mass felt. There was no murmur or thrill. Patient in shock	Died in 4 hours	Orange-sized, sacular aneurysm below superior mesenteric, adherent to third portion of duodenum, perforating latter
2	1859	Johnson ³	37	M	Back pain 1 year. Epigastric swelling 7 weeks	Pulsating epigastric mass to left of midline. No murmurs present	Mass enlarged, murmur developed over it. He had sudden hematemesis and died rapidly	Gumma of liver, aneurysm anterior wall perforating third portion of duodenum and eroding vertebrae
3	1862	Seligman ⁴	47	M	Colicky pain over kidney radiating down loin to testes, few days' duration	Firm, fixed mass about the navel	Died suddenly in bed, 6 months after onset of pain	Marked arteriosclerosis of abdominal aorta, with dilatation, adhesion to small bowel, and perforation
4	1874	Stich ⁵	Aged	F	Sudden hematemesis		Recurrence of hematemesis. Died in 2 weeks	Severe arteriosclerosis of abdominal aorta, dilatation, ulceration through this into adherent, adjacent third portion duodenum
5	1878	Von Velhling ⁶	74	F	Sudden collapse		Rapid death	Egg-sized sacular aneurysm fixed to and perforating third portion of duodenum. Severe arteriosclerosis present
6	1883	Compland ⁷	72	M	Weakness, loss of weight, about 3 months' duration. Sudden abdominal pain and collapse	Tender, pulsating, oval mass to right of midline. No bruit	Three months after first acute episode, had a second one associated with severe abdominal pain. Death sudden 5 days later	Sacular aneurysm, filled with thrombus, located below renal vessels, with perforation into third portion of duodenum. Marked arteriosclerosis present
7	1891	Dickenson ⁸	28	M	History of syphilis. Epigastric pain 6 months, backache and loss of weight. Sudden collapse, tarry stools		Three days before death, became jaundiced. Death occurred suddenly after profuse hematemesis	Large sacular aneurysm lying above the celiac axis, compressing the common duct and rupturing into second part of duodenum

8	1891	Bailey ⁹	45	M	Abdominal mass 2 years. Back pain 2 years. Sudden hematemesis and shock	Pulsating epigastric mass. Bruit present	Repeated hematemesis and death after 8 days	Large aneurysm perforating into stomach
9	1892	Bernachio	52	M	Abdominal mass many years. Pain about umbilicus, few days	Slightly tender pulsating mass felt in epigastrium	Awoke from sleep vomiting blood. Died after 8 days	Apple-sized aneurysm adherent to, and perforating, third portion of duodenum. Many arteriosclerotic plaques present
10	1893	Brannan ¹¹	73	M	Sudden attack of hematemesis		A second attack 2 days later was fatal	Aneurysm above renal artery adherent to and perforating third part of duodenum. Aneurysm filled with thrombus. Marked arteriosclerosis present throughout
11	1895	Fo ¹²	28	M	Three months before, penile ulcer. Inguinal abscess 2 weeks before admission. One week, lumbar pain	Epigastric mass felt	Sudden hematemesis day after admission and death in a few minutes	Perforation of aorta 2 cm. below renal arteries, leading into a false aneurysm which was adherent and had perforated into third part of duodenum. Streptococci were found in adventitia and surrounding tissues in region of perforation
12	1899	Boinet ¹³	28	M	Abdominal and lumbar pain	Expansile epigastric mass	Few weeks after admission had hematemesis, and rapid death	Egg-sized aneurysm lying above the superior mesenteric, adherent and perforating third portion of duodenum
13	1905	Locke ¹⁴	81	M	Severe lumbar pain, 3 months	Oval, pulsating epigastric mass	Sudden hematemesis, recurring 3 days later, and then death	Saccular aneurysm of abdominal aorta, partly filled with thrombus. It was adherent to, and had perforated, third portion of duodenum
14	1911	Celles and Jean-nency ¹⁵	61	M	Sudden hematemesis	Strongly pulsating mass felt in epigastrium	Death in 2 days	Aneurysm just above bifurcation of aorta, adherent to, and perforating, the jejunum
15	1913	Zyppin ¹⁶	45	M	Syphilis 12 years. Weakness, epigastric pain, melena	Tender, pulsating epigastric mass. Thrill felt. Murmur heard	Repeated, severe epigastric pain, tarry stools. Death in 8 days after admission	Walnut-sized aneurysm on anterior wall of aorta, adherent to, and perforating, stomach. Microscopic examination showed syphilitic mesoarteritis

TABLE I—CONT'D

DATE	AUTHOR	AGE	SEX	PERTINENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC CHANGES
16 1914	Tozer ¹⁷	32	M	Gradual onset of abdominal pain, getting progressively worse	Mass with expansile pulsation, seen and felt above and to left of umbilicus	One month after admission, hematemesis and rapid death	Saccular aneurysm arising below inferior mesenteric artery, perforating third portion of duodenum. Microscopic examination showed evidences of tuberculosis of aorta
17 1918	Marlow (Case 1) and Doubleris	39	M	Abdominal pain 6 months, weakness. Sudden onset of shock, hematemesis, and melena	Pulsating epigastric mass	A month later, second attack of hematemesis and death	Aneurysm, anterior wall of aorta, perforating into third portion of duodenum
18 1918	Marlow (Case 2) and Doubleris	81	M	Sharp pain in back	Pulsating abdominal mass	Sixteen days after admission had hematemesis and died	Aorta below renal arteries contained two aneurysms. One was adherent to, and perforated, third portion of duodenum
19 1921	Gerlach ¹⁹	20	F	Sudden hematemesis and death		Died promptly after onset of hematemesis	Mycotic saccular aneurysm, arising below superior mesenteric artery, was adherent to, and perforating, third portion of duodenum
20 1926	Kern ²⁰	49	M	Acute otitis media 5 months before admission, healing in 2 months. Continuous fever, fatigue, and lumbar pain since		Low-grade fever, with rises to 104°. Three weeks after admission severe hematemesis and death in 2 hours	A saccular aneurysm was found below superior mesenteric artery. Its surface was partially covered with thrombus. It was adherent to, and had perforated, third portion of duodenum
21 1928	Messary and Flandrin ²¹	53	M	Abdominal mass several months. Sudden hematemesis. History of syphilis and gumma of the testicle	Expansile, pulsating mass	Repeated hematemesis. Severe abdominal pain and death on seventh day	Aneurysmal dilatation adherent to, and perforating, third portion of duodenum
22 1928	Abava ²²	56	M	Syphilis at 21. Pulsating mass and severe pain in left upper quadrant, 6 months	Tender, pulsating mass	Recurrent hematemesis and death in 6 weeks	Aneurysm of abdominal aorta perforating the duodenum

23	1930	Feller ²⁴	27	M	Periodic furunculosis, sore throat, vomiting, and melena		Repeated vomiting and melena; death in 9 days	Mycotic aneurysm at level of celiac axis adherent to, and perforating, the stomach
24	1931	Pescador and Villanueva ²³	32	F	Sudden hematemesis	Epigastric mass, murmur, and thrill. Serologic reaction positive	Repeated hematemesis; death on seventh day	Aneurysm of aorta adherent to cardia of stomach with perforation into it
25	1931	Riggs and Massey ²⁵	69	M	Weakness and backache 8 months. Sense of burning in epigastrium 2 months. Sudden melena	Epigastric mass. Serologic reaction negative	Day after melena went into shock and died	Saccular aneurysm 2 cm. above bifurcation, filled with thrombus, adherent to, and perforating, the duodenum
26	1936	Scully ²⁶	62	M	Entered hospital with malaria		Month after admission, abdominal mass developed, also severe abdominal pain, melena, shock, and death	Saccular aneurysm, adherent to duodenum. Perforation into third portion
27	1936	Kampmeier ²⁷			No data	No data	No data	Aneurysm of celiac axis rupturing into stomach
28	1937	Manson ²⁸	76	M	Found in shock	Pulsating mass in epigastrium	Death in 2 days	Saccular aneurysm of anterior wall, adherent to, and perforating, third portion of duodenum
29	1937	Neely (Case 3) ²⁹	59	M	Intermittent dysuria, frequency, nocturia	Pulsating mass in right flank	Sudden shock and hematemesis; death in 2 days	Aneurysm of lower abdominal aorta ruptured into retroperitoneum, producing a false aneurysm which in turn became adherent to, and perforated, third portion of duodenum
30	1939	Roach ³⁰	52	F	Long history of digestive trouble typical of peptic ulcer. More recently, severe epigastric pain and hematemesis		Repeated hematemesis and death	Abdominal aorta was markedly calcified. Aneurysm present, eroding third portion of duodenum
31	1941	Smith ³¹	77	M	One week, indigestion and vomiting. Hematemesis day before admission	Pulsating mass to right of umbilicus	Two hours after admission, shock and death	Marked arteriosclerosis of aorta, with a saccular aneurysm, filled with thrombus, adherent to, and perforating, third portion of duodenum

dominal aneurysm, should be considered, although in this particular case very little atherosclerosis was found. There is a possibility, of course, that it might have been particularly severe at the site of aneurysm formation, and subsequently became obscured by ulceration and thrombus formation. This, however, would be most unusual, for it is the rule that atherosclerosis is present to a rather severe degree both in and beyond the aneurysm, and remains detectable despite thrombus formation. A final possibility is mycotic aneurysm. The presence of organisms in our case complicates rather than clarifies matters. Unfortunately, cultures were not made, so that one has only morphologic criteria for identification of the bacteria. They were large, Gram-positive bacilli, some of which contained spore-like vacuoles. The resemblance to *B. subtilis* was close. The problem is made more perplexing by the fact that the organisms were found in the wall of the aneurysm and on the surface of the thrombus which filled it, and in no other place in the body, thus eliminating the possibility of ante- or post-mortem bacteremia. A probable reason for the peculiar localization is that the organism reached the aneurysm via the duodenal perforation. More suggestive of a mycotic origin is the fact that there was an antecedent history of pneumonia, complicated by empyema, and later by destructive arthritis of the hip joint. It was during a three months' stay in bed for this condition that the aneurysm was discovered and subsequently seen to grow and finally to rupture. Unfortunately, we were not able to demonstrate cocci. Of the cases collected (Table I), in only four was the aneurysm reported as mycotic.^{12, 19, 20, 24} The stories of these are as follows:

Case of Foá:¹² The patient was a 28-year-old man. A week before admission he had a right inguinal abscess, fever, and pain in the lumbosacral area. After incision and drainage the abscess healed, but the pain persisted. Physical examination disclosed a tender, protuberant abdomen. An orange-sized mass was felt in the epigastrium. After four days of diarrhea he vomited blood and died. Necropsy disclosed a false aneurysm which communicated with the aorta on the one hand, and the third portion of the duodenum on the other. Microscopic examination disclosed streptococci throughout the adventitia, in the periaortic tissue, in the walls of the aneurysm, and in the serosa of the duodenum. Small abscesses were also found in the adventitia of the aorta. The author concluded that, with the inguinal abscess as a focus, the infection spread to the prelumbar lymphatics, producing a periaortic cellulitis which, in turn, infected the wall of the aorta and led to aneurysm formation.

Case of Gerlach:¹⁹ The report concerned a 20-year-old woman. She had abdominal pain and died of hematemesis. Autopsy revealed a sacular, false aneurysm between the superior and inferior mesenteric arteries; it was adherent to the duodenum and had ruptured into it. Because of a history of throat infection shortly before, the patient's youth, and the lack of other etiologic factors, it was concluded that the aneurysm was mycotic.

Case of Kern:²⁰ The patient was a 49-year-old man who developed acute otitis media with a high fever. The condition persisted for two months. After this he continued to be weak, had low-grade fever, and developed a burning pain in the lumbar region. Three weeks before admission he developed an intermittent fever which reached 104° F. Physical examination failed to disclose a focus of infection. After a febrile course of three weeks he began to vomit blood and died. At the

autopsy an abscess containing about two ounces of pus was found in the region of the bifurcation of the aorta. At this point the wall of the aorta tore easily. In addition, an opening, $2\frac{1}{2} \times 3\frac{1}{2}$ cm., was found higher up in the aorta, and led into an aneurysm. The latter, in turn, was adherent to the third portion of the duodenum and communicated with its lumen. The author was not sure of the cause of the aneurysm in this case. He felt that it might be mycotic.

Case of Feller:²⁴ The patient was a 27-year-old man who was operated on for duodenal ulcer. He subsequently died. Autopsy disclosed an aneurysm above the celiac axis which was adherent to, and communicated with, the stomach. Microscopically, Gram-positive cocci, in chains, were discovered in the fibrin and polymorphonuclear leucocytes which covered the inner surface of the aneurysm. The author concluded that the aneurysm was mycotic in nature. Later, he obtained a history that the patient had had furunculosis one and one-half years before, and, a year later, tonsillitis. Five months after this he developed severe backache and fever.

Since only these four cases have been reported, it is apparent that rupture of a mycotic abdominal aneurysm into the gastrointestinal tract is rare. Careful scrutiny shows that in only two of the above cases was the diagnosis apparently proved; in the others it was doubtful. It is possible that our case falls in the doubtful group.

Regardless of cause, other features of the case are of interest. One of these is the fact that the usual site for rupture into the gastrointestinal tract is the third portion of the duodenum. The reason for the particular predilection for this part of the intestine lies in the fact that it is relatively fixed, so that it is not as easily displaced by a gradually enlarging tumor as are the stomach and small intestine. The pressure of the aneurysm produces irritation which leads to fibrous adhesions, and, eventually, to focal necrosis of the duodenum. Subsequently, digestive juices probably play a part in accelerating the perforation of the one organ into the other.

SUMMARY

1. Thirty-one cases of rupture of an abdominal aneurysm into the stomach and duodenum were collected from the literature.
2. The clinical and pathologic data on these cases are presented in table form.
3. Four cases of what was probably mycotic aneurysm were collected from the literature and are described.
4. Another case of aneurysm which may have been mycotic is reported; in this instance the aneurysm ruptured into the duodenum.

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CONGENITAL SUBAORTIC STENOSIS, WITH DEFORMITY OF THE AORTIC VALVE

REPORT OF A CASE WITH COMPLICATING SUBACUTE BACTERIAL ENDOCARDITIS AND MYCOTIC ANEURYSM RESULTING IN RUPTURE OF
THE AORTA INTO THE PERICARDIUM

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D. C., AND PAUL D. WHITE, M.D., BOSTON, MASS.

AMONG the rarer types of congenital heart disease is subaortic stenosis. Abbott¹ described twelve instances among one thousand cases of congenital heart disease. Wiglesworth² found only thirty-six in a review of the literature prior to 1937, to which he added one case. No instances of this congenital anomaly have been found in more than ten thousand autopsies at the Massachusetts General Hospital.³ Because the reported cases of subaortic stenosis are so few, and because subaortic stenosis may be confused clinically with acquired aortic valve disease, chiefly rheumatic in type, as it was in this case, we are adding this report to the literature. Congenitally deformed aortic valves, per se, are occasionally seen at post-mortem examination, but we have found in the literature only one other case in which a congenitally deformed (bi-cuspid) aortic valve was associated with subaortic stenosis. In that case, reported by Thursfield and Scott,⁴ there was probably, also, slight coarctation of the aorta. It is of further interest that the death of our patient was the result of cardiac tamponade from rupture of a mycotic aneurysm within the pericardial sac.

CASE REPORT

Mrs. C. was first seen by one of us (P. D. W.) in 1929, at the age of 17 years, when a diagnosis of rheumatic, or, possibly, congenital, heart disease, aortic stenosis, and slight aortic regurgitation was made. There was no clear-cut history of rheumatic fever. She was examined for the second time ten years later, during the early part of pregnancy. The heart was essentially the same as ten years before. Pregnancy was borne without difficulty, and she was in excellent health in April, 1939, after the forceps delivery of a healthy baby. She continued well, leading a moderately active life without discomfort, until April, 1940, when there appeared, two weeks after extraction of a tooth, unusual fatigue, chills and fever, and diarrhea. There developed considerable pain, tenderness, and swelling of several large joints. She was studied carefully in order to ascertain the nature of the infection, and a diagnosis of subacute bacterial endocarditis was made, with positive *Streptococcus viridans* blood cultures, some weeks thereafter. She was given sulfapyridine, but did not tolerate it well, and the drug was discontinued because of much nausea and vomiting and the development of moderately severe anemia. The course of the disease was a slowly progressive one. She showed increasing pallor, continuous fever, and severe asthenia.

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On Jan. 6, 1941, she was seen by one of us (B. J. W.) because of the sudden onset of severe pain beneath the upper part of the sternum and left clavicle. On examination she showed numerous petechiae, particularly over the soles of the feet and in the conjunctivae, marked pallor, and scattered pulmonary râles, particularly on the left side, behind the heart. There was moderate enlargement of the liver; this had not been present before. The spleen was readily palpable, as it had been since April, 1940. There was no edema or shortness of breath. She was able to lie flat without distress. On examination of the heart there was heard a loud, rough systolic murmur, maximal in the aortic area to the right of the sternum, but well heard over the entire chest, and accompanied by a thrill. There was a slight blowing diastolic murmur along the left sternal border. The heart was much enlarged; the apex impulse was visible 11 cm. to the left of the midsternal line in the fifth intercostal space. The aortic second sound was present, but greatly diminished. The blood pressure measured 100/70.

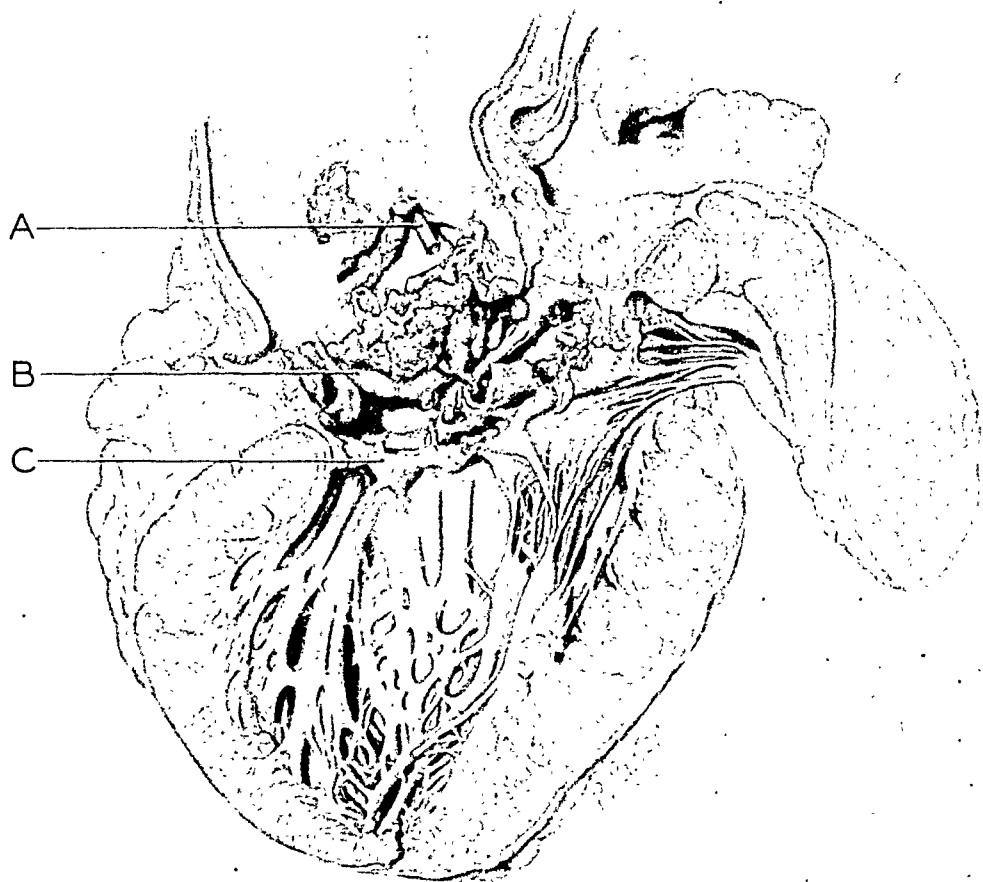


Fig. 1.—Drawing of opened left ventricle and first part of aorta. A, Internal opening of mycotic aneurysm, with probe inserted. B, Aortic valve, with vegetations. The arrow points to the large posterior cusp, on each side of which there are small anterior cusps separated by an elongated raphe which is hidden at the left-hand side of the drawing; about half of each anterior cusp is visible in the drawing, flanking the large posterior cusp. C, Subaortic shelf.

Death occurred suddenly twenty-four hours later, apparently not preceded by pain or other unusual circumstance.

Autopsy was performed five and one-half hours after death. When the thoracic plate was removed, there was evident a bluish color of the pericardium. The pericardium was opened, and 500 c.c. of blood were found therein, mostly in a large clot.

The heart and lungs were removed, and, after careful search, there was found, about 2.5 cm. above the aortic ring, a small aneurysmal dilatation of the aorta 2.5 cm. in length, at one end of which was a point of rupture from which blood could be expressed. The rupture was about the size of the end of a probe. Freed of the blood in the pericardium, the heart weight was approximately 425 grams.

The heart was opened, first into the left auricle, which seemed slightly dilated. Just above the mitral valve there was a small group of firm vegetations about the size of a pea. The valve leaflets and the remainder of the valve were entirely normal. There were no evidences of auriculitis. When the left ventricle was opened a considerable degree of infundibular stenosis was found 1.5 cm. below the insertion of the aortic valve; this was accentuated still further by a firm, raised fibrous ridge, 4 mm. wide and 4 mm. high, encircling the vestibule of the aorta and resulting in the formation of a small chamber between the aortic cusps and the subaortic shelf. There was a considerable mass of friable, irregular vegetations attached to the aortic valve cusps, and small clumps of the same type were found on the subaortic shelf. The probe was pushed gently through the external orifice of the aortic rupture, and protruded into the lumen of the aorta through the interior opening of a mycotic aneurysm which had developed beneath a plaque of vegetations about 2 cm. above the posterior cusp of the aortic valve. The left ventricle was considerably thickened; its wall measured about 15 mm. in section. The aortic valve was congenitally deformed; there were one very large posterior cusp, about 3 cm. in width, and two small anterior cusps of about equal size ($1\frac{1}{2}$ cm. each), which were equal to, or a little smaller than, the one large cusp. The coronary mouths were normally placed, one behind each of the anterior cusps. The valve, where it was free of vegetations, appeared normal, without evidence of rheumatic infection, past or present. The valvular endocarditis was preponderantly situated on the large posterior cusp.

The lungs were dry and entirely normal, except for a small area of atelectasis in the left lower lobe. There was no evidence of pericarditis or pleuritis. There were 500 c.c. of clear yellow fluid in the right pleural cavity.

The liver was considerably enlarged (estimated weight, 2,500 grams), and purplish-red; section showed that it contained an increased amount of blood. Otherwise the appearance was normal.

The spleen was much enlarged (estimated weight, 600 grams). There was a large, pyramid-shaped, healed infarct on the diaphragmatic surface of the spleen.

The kidneys did not appear remarkable except for two or three old infarcts. The bowel was removed and opened; it revealed nothing unusual.

Microscopic examination showed numerous collections of inflammatory cells in the myocardium. In some areas these were so numerous as to constitute abscesses. No definite Aschoff bodies were seen. There were the usual microscopic changes associated with areas of infarction in the spleen and kidney. There was marked chronic passive congestion of the liver. No histologic studies were made of the subaortic shelf or of the aortic valve. Nothing else of importance was found.

DISCUSSION

There has been some controversy concerning the nature and origin of the firm, raised ring of tissue beneath the aortic valve which gives rise to the anomaly known as subaortic stenosis. The most reasonable explanation seems to be that presented by Sir Arthur Keith,² in whose opinion this firm, raised band is of congenital origin and represents a remnant of the bulbus cordis. Histologic evidence in the case described by Wiglesworth is in keeping with this point of view.

Subaortic stenosis may be suspected in patients under 20 years of age when there is no clear-cut history of rheumatic fever and the patient presents the auscultatory signs of well-developed aortic stenosis and a normal or nearly normal aortic second sound, for acquired stenosis of the aortic valve seldom occurs in patients under the age of 20 years. In the presence of these signs, the younger the patient, the more likely is the diagnosis of congenital subaortic stenosis to be correct.

The slight diastolic murmur along the left sternal border in our case probably resulted from the deformity of the aortic valve, for slight aortic regurgitation may have been present, although, as a rule, a bicuspid aortic valve does not produce a murmur. This was apparently true in the case described by Thursfield and Scott,⁴ for, in their report of a case of bicuspid aortic valve and subaortic stenosis, no diastolic murmur was mentioned.

SUMMARY

A case of congenital subaortic stenosis, with a congenitally deformed aortic valve, is described; the patient was a woman who died, at the age of 29 years, of subacute bacterial endocarditis, with a ruptured mycotic aneurysm of the aorta and cardiac tamponade. We believe that a correct diagnosis of congenital subaortic stenosis is possible in patients under the age of 20 years who show clinical evidence of aortic stenosis, with a normal or nearly normal aortic second sound.

We are indebted to Dr. Eugenia E. Murphy, of Arlington, Va., for her cooperation concerning this case.

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4. Thursfield, H., and Scott, H. W.: Sub-Aortic Stenosis, *Brit. J. Child. Dis.* 10: 104, 1913.
5. Keith, Sir Arthur: Schorstein Lecture on the Fate of the Bulbus Cordis in the Human Heart, *Lancet* 2: 1267, 1924.

Abstracts and Reviews

Selected Abstracts

Eggleton, M. G., Richardson, K. C., Schild, H. O., and Winton, F. R.: Renal Impairment Due to Crushing Limbs in Anaesthetized Dogs. *Brit. M. J.* 2: 392 1942.

So far as available evidence goes, the injury to the kidneys in this series of dogs appears to be of the same kind as that in man after comparable prolonged crush injury to the limbs. The essential nature of the renal damage has not yet been determined, but the evidence suggests that the main factor may be concerned with increase in permeability of the renal tubules due to a toxic agent released from the damaged limbs, while there may be an additional factor involving reduction in the rate of glomerular filtration probably due to lowering of glomerular capillary pressure.

AUTHORS.

Davies, F.: The Conducting System of the Vertebrate Heart. *Brit. Heart J.* 4: 66, 1942.

The specialized muscle fibers comprising the conducting system of the hearts of mammals and birds include S-A node, A-V node, A-V bundle and its two limbs, and terminal ventricular subendocardial and penetrating Purkinje fibers. Added to these in the bird's heart are the atrial subendocardial and penetrating Purkinje fibers, the right A-V ring, and the special branch of the right limb of the A-V bundle to the muscular A-V valve.

While the main topography of this system is similar in mammals and birds, differences are correlated with functional requirements.

The specialized cardiac conducting system of these homoiothermal vertebrates is not a remnant of more extensive tissues of similar structure in lower vertebrate hearts. It is a neomorphic development, associated with the more rapid rate of the heart (more rapid, in proportion to its size). Ontogenetic development of these structures in the mammal (calf) supports this view.

In a lowly generalized vertebrate heart (salamander) no specialized tissue is present. The sequences of the cardiac cycle are similar to those of the higher vertebrates. Each chamber has its own intrinsic rhythmic rate, the reason for which is not clearly established. The glycogen content of the musculature of the heart of the frog, which is also devoid of specialized tissue, is inversely proportional to the intrinsic rhythmic rates of the several chambers. In mammals and birds, parallel evolution of the specialized conducting system has taken place; small differences in the topography of the specialized conducting fibers in closely allied species, or in different animals of the same species, may be attributed to variation.

AUTHOR.

Sharpey-Schafer, E. P., and Wallace, J.: Circulatory Overloading After Rapid Intravenous Injections. *Brit. M. J.* 2: 304, 1942.

Up to 2,000 c.c. of saline, serum, and blood was injected into subjects without cardiovascular disease at rates of from 54 to 168 c.c. a minute. The venous pressure was raised up to 11 cm. H_2O when there was considerable retention of injected fluid in the circulation, as indicated by the fall in hemoglobin. Radiographs showed an increase in the diastolic size of the heart, enlargement of the pulmonary arteries, and prominence of the vascular markings in the lung fields. Vital capacity was diminished, but there was no evidence of pulmonary edema. In spite of the rise of venous pressure many subjects had no increase in heart rate. Of twelve subjects four showed electrocardiographic changes indicating slight right heart stress. Symptoms were absent or unimportant. There was a rapid fall of venous pressure to normal on ceasing injection, except in one subject given blood. There is evidence that the peripheral and pulmonary capillaries and veins dilate to accommodate the increased blood volume.

When the blood volume was first reduced by a large venesection, saline or serum injected in similar amounts and at similar rates caused little or no rise of venous pressure.

AUTHORS.

Hass, G. M.: Elastic Tissue. II. A Study of the Elasticity and Tensile Strength of Elastic Tissue Isolated From the Human Aorta. *Arch. Path.* 34: 971, 1942.

In a series of twenty-one human aortas, aged 10 days to 77 years, the amounts of elastic tissue which were recovered varied from 28.9 to 42.2 per cent, with an average of 37.9 per cent.

The quantity of elastic tissue in each unit volume of the average aortic wall remains nearly constant throughout life. Individual variations are included in the range 28.9 to 42.2 per cent.

The purified elastic systems possess an average of 32 per cent greater extensibility and 170 per cent greater retractility than the intact aortic walls from which they are isolated.

The average maximum extensibility of isolated elastic tissue decreases with increasing age in a manner which cannot be predicted by a study of the intact aorta.

The retraction of isolated elastic tissue after extension is always more complete than that of the intact vessel. The magnitude of retraction is the same for all isolated networks and is independent of their age.

The tensile strength of isolated tissue varies from 1,490 to 6,750 Gm. per square centimeter of dry cross-sectional area at maximum extension. In general, tensile strength decreases with increasing age. There are several unexplained exceptions to this average rule.

AUTHOR.

Henry, F.: Cardiovascular Effects of Experimental Insomnia. *Am. J. Physiol.* 138: 65, 1942.

The mean heart rate of eight male human subjects was lowered at rest in the reclining posture but not while standing, as the result of twenty-four hours of sleep deprivation. It was also lowered during exercise and recovery. An increased negative phase was observed, and there was also a reduction in the amount of relative bradycardia produced by a modified Valsalva experiment performed during early recovery from exercise. A reduced irritability of some part of the mechanisms responsible for rate control during late exercise and recovery is postulated in explanation.

Scores on the Foster, pulse-ratio, and McCurdy-Larson cardiovascular tests were markedly improved as a result of the insomnia. The Schneider index was also raised, but the increase was not statistically significant.

Kisch, B., Goldbloom, A. A., and Zucker, G.: Electrocardiographic Changes After Occlusion of the Pulmonary Artery or Aorta. *Cardiologia* 6: 83, 1942.

Experiments are presented in which an acute increase in pressure in one ventricle was produced by clamping the pulmonary artery or aorta. Typical electrocardiographic changes were observed.

These electrocardiographic changes are similar to those recently described after a potassium chloride blotting paper was placed on an isolated area of the right or left side of the heart respectively. These findings seem to indicate that in these experiments a damage of predominantly one side of the heart is present.

No electrocardiographic changes were obtained in the authors' experiments when one hilus or when less than two-thirds of the pulmonary artery was clamped.

AUTHORS.

Kisch, B.: A Contribution to the Problem of the Electrical Alternation of the Heart. *Cardiologia* 6: 95, 1942.

It is shown that the presence of alternation in the electrocardiogram depends in the same way on exactly the same factors as the mechanical alternation of the heart manifest in the tracings of heart beat and pulse wave.

These important factors are the bioenergetic condition of the heart (disposing factor), the heart rate, the blood pressure and the extracardiac nerves of the heart.

There is no reason to look at the electric alternans as a separate phenomenon of the heart pathology as was repeatedly done in the literature of the last years.

A satisfactory explanation of the isolated electric alternans is given by recent findings that only or predominantly the surface layer of the heart muscle is shaping the eeg. from the peak of R up to the end of T.

A tracing is presented which shows an alternating A-V conducting time in a cat's heart.

AUTHOR.

Nylin, G., and Crafoord, C.: Simultaneous Electrograms From Left and Right Ventricles of the Human Heart. *Cardiologia* 6: 136, 1942.

Simultaneous, selective (unipolar) electrograms of the right and left ventricles of the freed human heart with intact pericardium give potential and typical dextro-respectively sinistrograms opposed to each other.

AUTHORS.

Dagnini, G.: Gallop Rhythm and Atrioventricular Dissociation. *Cardiologia* 6: 146, 1942.

Description of three unusual forms of gallop rhythm caused by atrioventricular dissociation. The author suggests the first form be termed retarded proto-diastolic gallop, the second variable proto-meso-tele-diastolic gallop and the third variable pre-diastolic-meso-proto-diastolic gallop. Each term gives the characteristic beat in the acoustic sense, as also the special aspect expressed in the tonogram. The first type is observed with partial A-V block of the type 2:1, the second with complete A-V dissociation, the third with partial block with Wenckebach-Luciani's periods.

The conditions under which each form arises are enumerated and individual points, which partly explain the genesis of the tones connected with the disturbances mentioned, are emphasized.

AUTHOR.

Edeiken, J.: Extreme Tachycardia: With Report of Non-Fatal Paroxysms Following Myocardial Infarction. Am. J. M. Sc. 205: 52, 1943.

Two cases of extreme tachycardia are added to the fifteen cases previously reported with a recorded ventricular rate of 300 or more per minute; in one instance the tachycardia occurred during the acute stage of myocardial infarction.

So far as can be determined, Case 1 is the only case in which such extreme tachycardia was recorded in the presence of acute myocardial infarction; in the other cases of extreme tachycardia the myocardium was regarded as sound.

Two paroxysms of extreme tachycardia occurred in the patient suffering from myocardial infarction—one lasting twelve hours with a ventricular rate of 310 per minute, and another lasting thirty-four and one-half hours with a ventricular rate of 303 per minute. The onset and offset in both attacks were sudden.

The ventricular rate of 310 per minute is the fastest sustained tachycardia recorded in the adult human heart; more rapid rates have been recorded in infants.

In nine of the fifteen previously reported cases, treatment did not appear to influence the paroxysms or prevent their recurrence. It is questionable whether treatment (quinidine and digitalis) exerted any beneficial effect in stopping paroxysms complicating acute myocardial infarction.

AUTHOR.

Toledo, P. de A.: Sinoauricular Block. Rev. argent. de cardiol. 9: 111, 1942.

Numerous arguments, clinical, physiopathologic and experimental, are in favor of the existence of sinoauricular block. Following Spuehler, many electrocardiographic records of difficult interpretation may be considered as an example of this type of block.

Sinoauricular blocks may be classified in the same way as auriculoventricular blocks. They are generally reversible, of vagal or toxic cause or combination of both, and their differential diagnosis is facilitated by the exercise and atropine tests. Sometimes they coexist with other conduction disturbances in which case severe and diffuse myocardial lesions are probably present.

AUTHOR.

Vedoya, R., Videla, J. G., and Albanese, A. R.: Persistence of the Ductus Arteriosus. Surgical Intervention in Four Cases. Rev. argent. de cardiol. 9: 94, 1942.

The results obtained by ligation of the ductus in four cases of patent ductus arteriosus are reported. Two of them were in bad condition when operated upon. The results were excellent in the three cases in which no other malformation was present. Marked reduction of the heart size a few days after operation, great improvement of functional capacity of the heart and beneficial effects on somatic and intellectual development were the salient features.

One case, in which a pulmonary stenosis was diagnosed during operation, died a few hours after of pulmonary embolism.

On discussing its indication, the conclusion is reached that operation should be tried in every case, and as early as possible.

AUTHORS.

Corner, B., and Perry, B.: Hemiplegia in Cyanotic Congenital Heart Disease. Brit. Heart J. 4: 121, 1942.

Three cases of cyanotic congenital heart disease developing sudden hemiplegia in infancy have been described. The possible mechanism of this has been discussed.

AUTHORS.

Cossio, P., Dambrosi, R. G., and Lezica, A. P.: Cardiac Aneurysm and Isolated Myocarditis. Rev. argent. de cardiol. 9: 182, 1942.

In a case of isolated myocarditis necropsy revealed the presence of a parietal aneurysm next to the apex of the heart. In the absence of other etiologic evidences, especially of coronary lesions, and considering the predominance of infiltrates at the level of the aneurysm, a relation of cause and effect between isolated myocarditis and aneurysm is established.

AUTHORS.

Cookson, H.: Fainting and Fits in Cardiac Infarction. Brit. Heart J. 4: 163, 1942.

Among two hundred patients with acute cardiac infarction, a syncopal or epileptiform attack was observed in fifteen. At the onset syncope occurred in ten, of whom five were aged 70 years or more. They presented the appearance of severe peripheral circulatory failure, often combined with a slow heart rate, but in one there was ventricular tachycardia. Pain might be absent or slight. In five, the cardiogram showed abnormal rhythms of supraventricular origin. Posterior infarction was commoner than anterior. Six of the patients had died by the fourth month. Possible causes of the syncope are briefly discussed.

Syncope and fits in the course of cardiac infarction are reported in five patients, whose average age was 69 years. Two had suffered previously from anginal pain. Two had syncope and three had Stokes-Adams attacks. All five died within twenty-nine days of onset. Abnormal rhythms were recorded in four. Cardiograms during the actual attack showed complete heart block in one, and nodal rhythm with a change in the ventricular complex immediately after a short convulsion in another. Indirect evidence as to the mechanism underlying the attacks in the remaining cases is given.

AUTHOR.

Rascoff, H.: Beriberi Heart in a 4-Month-Old Infant (With Four-Year Follow-Up). J. A. M. A. 120: 1292, 1942.

In a case of beriberi heart in a 4-month-old infant the diagnosis was made clinically, and therapeutic response was noted with thiamine hydrochloride. The daily diet of the average young infant is deficient in thiamine hydrochloride and should be supplemented with vitamin B₁. In cases of gastrointestinal disturbances the vitamin B₁ intake is to be increased.

Some cases at present diagnosed as idiopathic cardiac hypertrophy, or deaths attributed to status thymicolymphaticus, may be caused by infantile beriberi.

AUTHOR.

Kuttner, A. G., and Beyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide. J. Clin. Investigation 22: 77, 1943.

Streptococcal upper respiratory infections and rheumatic relapses in rheumatic children were prevented by the prophylactic administration of sulfanilamide.

Toxic manifestations of sufficient severity to necessitate the withdrawal of the drug occurred in 15 per cent of the patients.

Children, who did not develop toxic reactions, tolerated the drug well.

The effectiveness of sulfanilamide in preventing rheumatic recurrences indicates that infection with Group A hemolytic streptococci is an important factor in the etiology of rheumatic fever.

AUTHORS.

Guion, C. M., and Adams, E. C.: Six Autopsied Cases of Disseminated Lupus Erythematosus. *Am. J. M. Sc.* 205: 33, 1943.

The clinical, laboratory, and autopsy findings in six cases of disseminated lupus erythematosus observed at the New York Hospital between 1936 and 1940 are reported.

No common etiologic basis was observed in these six young women. Study of the diseased tissues cast no light on the pathogenesis.

While vascular lesions were observed, none of the cases resembled periarteritis nodosa. Noteworthy was the frequent association with acute and chronic arthritis and with pericarditis.

AUTHORS.

Christian, H. A.: Nonspecificity of Glomerular Lesions of the Kidney. *Am. J. M. Sc.* 204: 781, 1942.

This paper has emphasized the nonspecificity of lesions observed in the glomerulus of the kidney and offers this nonspecificity as an explanation of many similarities in the signs and symptoms of renal diseases.

AUTHOR.

Howell, T. H.: Blood Pressure and Old Age. *Brit. Heart J.* 4: 143, 1942.

A rise of systolic blood pressure is common after the age of 60 years.

In the present series of 120 Chelsea pensioners, 42 per cent had systolic figures regularly over 160 mm.

Cancer, cardiac failure, and infections often cause a fall in blood pressure.

Marked arteriosclerosis, in the absence of raised blood pressure, is usually associated with poor physical condition.

It is suggested that the raised blood pressure of old age is a form of compensation tending to prevent ischemia of vital structures.

AUTHOR.

Redish, J., and Chasis, H.: Function of the Separate Kidneys in Hypertensive Subjects. *Arch. Int. Med.* 70: 738, 1942.

The impairment of renal parenchyma in hypertensive subjects proceeds in a parallel manner in both kidneys, the pace varying in different persons. The decrease in renal blood flow is shared equally by the two kidneys. In twenty-one subjects with essential hypertension selected at random unilateral renal ischemia was not found to be present in a single instance.

Absolute reduction in blood flow to one or both kidneys, as measured by diodrast clearance, does not necessarily demonstrate that renal ischemia is present. This conclusion can be drawn only if the tubular excretory mass is measured, so that the blood flow per unit of tubular excretory tissue can be evaluated.

Many common variations in ureteropyelograms are believed to be without significance. Pyelographic abnormalities are not necessarily associated with functional disparity, and conversely, marked functional disparity may not be associated with pyelographic abnormalities.

The rate of reabsorption of water by the tubules and hence the rate of urine flow may vary markedly in two kidneys of equal functional capacity. Excretory tests comparing the function of the two kidneys should therefore be evaluated with caution, for inequality in urine flow of itself can account for variations in specific gravity of the urine, in appearance time and relative concentration of dyes and in the roentgen shadows in excretory pyelography.

In three hypertensive subjects who had undergone surgical procedures for renal conditions significant disparities in the blood flow to the two kidneys were observed. In one subject who had undergone bilateral splanchnicectomy the blood flow was less than normal in both kidneys and markedly so in one. In two subjects who had had unilateral operations (omentopexy and nephropexy) the blood flow to the treated kidney was less than that to the untreated kidney. In none of the three subjects did the elevated arterial tension fall after surgical therapy.

AUTHORS.

Feldt, R. H., and Wenstrand, D. E. W.: *The Family History in Arterial Hypertension: A Study of 4,376 Insurance Examinations.* *Am. J. M. Sc.* 205: 61, 1943.

A brief review of the literature and analysis of family histories taken from life insurance examinations are reported. In this series of 4,376 applicants, the incidence of familial cardiovascular disease was only slightly greater among hypertensive persons than it was among persons with normal blood pressure. There was no significant difference in the familial incidence of diabetes. It appears unlikely that heredity is of primary importance in the etiology of hypertension.

AUTHORS.

Lewis, T., and Stokes, J.: *A Curious Syndrome With Signs Suggesting Cervical Arteriovenous Fistula, and the Pulses of Neck and Arms Lost.* *Brit. Heart J.* 4: 57, 1942.

A patient is described in whom the pulses of the neck and arms had been lost, and who presented signs suggesting an arteriovenous fistula at the root of the neck. The defective blood supply to the upper parts of the body was responsible directly or indirectly for a gross defect of vision, for frequent fainting attacks and headaches, and for pain in the right arm during work. The blood pressure in the patient's legs was raised.

Another case of a very similar kind is described, and a third recorded by Giffin is compared with them.

The three cases show so much in common as to suggest a pathological entity hitherto unrecognized and still awaiting dissection before its precise form can be understood.

AUTHORS.

Rich, A. R.: *The Role of Hypersensitivity in Periarthritis Nodosa.* *Bull. Johns Hopkins Hosp.* 71: 123, 1942.

Vascular lesions characteristic of periarthritis nodosa have been found (1) in the viscera of five patients who, shortly before death, had had hypersensitive reactions following therapeutic injections of foreign serum. Four of these patients had received sulfonamides, but in at least two of those cases the evidence indicates that

the hypersensitive reaction was serum sickness and not drug sensitivity. The fifth patient had serum sickness in the absence of sulfonamide therapy; (2) in a biopsy of muscle from a patient who had a hypersensitive reaction following foreign serum and sulfonamide therapy; (3) in the viscera of a patient who had received prophylactic sulfonamide therapy against aspiration pneumonia.

None of these patients had had any symptoms suggestive of periarteritis nodosa prior to their terminal acute illness for which the serum or sulfonamide was administered, and the vascular lesions were fresh.

These cases, together with other pertinent evidence discussed in the body of this paper, indicate that vascular lesions of this type can be a manifestation of the anaphylactic type of hypersensitivity, and suggest the importance of a search for the inciting antigen in cases of periarteritis nodosa that come under clinical observation.

AUTHOR.

Master, A. M., Dack, S., and Jaffe, H. L.: Cardiac Efficiency and Prognosis Following Recovery From Acute Coronary Occlusion: The Results of Various Functional Tests. *J. A. M. A.* 120: 1271, 1942.

Cardiac efficiency was studied by various function tests performed serially on two hundred and two patients, who were observed for two to eight years following recovery from acute coronary occlusion. The results were evaluated from a prognostic point of view.

Recovery from acute coronary occlusion was found to be good or complete in over one-third of the patients; i.e., they had no symptoms of diminished cardiac reserve or routine activity. One-half were able to return to work, usually full time, and cardiac reserve, as measured by function tests, was normal or only slightly abnormal.

A persistent reduction in vital capacity was rare in the good recovery group, but common in those whose recovery was poor. However, the vital capacity not infrequently was normal in the presence of severe angina pectoris. A reduction below 2,000 c.c. was generally found only among patients who were in congestive heart failure.

The two-step exercise tolerance test, a simple nonstrenuous test of cardiac function, became normal in 18 per cent and remained distinctly abnormal in two-thirds of the patients. Return to normal usually occurred one or two years after the attacks, and was associated with a good clinical recovery and decreased incidence of subsequent attacks.

The teleoroentgenogram revealed definite cardiac enlargement in half of the patients, and the majority of these were hypertensive. As a general rule, chronic coronary sclerosis or coronary occlusion did not produce cardiac enlargement unless hypertension or heart failure was present. Although a severe degree of coronary disease may exist without cardiac enlargement, clinical recovery was more complete and subsequent attacks were less common when the heart size was normal, emphasizing the relation between heart size and cardiac function. Cardiac enlargement was always permanent.

A systolic expansion of the left ventricle, pathognomonic of previous infarction, was observed fluoroscopically or roentgenkymographically in nearly three-fifths of the patients, and localized absence or diminution of pulsation in 25 per cent. With few exceptions these abnormalities were permanent. Although an abnormal ventricular pulsation did not preclude a good recovery from the attack, it was almost universal in those whose recovery was poor. Not infrequently it was the only remaining sign of previous infarction, being observed in the majority of patients whose

electrocardiogram returned to normal. The patients with normal pulsations usually recovered completely, and rarely sustained another attack.

The electrocardiogram returned to normal or almost normal in 21 per cent of the patients, usually within one year after the attack. The great majority of these made a good recovery, as well as those whose T waves became normal although the Q waves persisted. However, the persistence of the findings characteristic of previous infarction, which was observed in almost two-thirds of the patients, was not necessarily a bad prognostic sign. The location of the infarct, i.e., whether anterior or posterior, did not affect the clinical course. However, when infarction of both surfaces had occurred, the prognosis was worse.

The electrocardiogram after the standard two-step exercise revealed signs of coronary insufficiency (depression of RS-T or inversion of T wave) in five of eighteen patients whose control record was normal, and in twenty-four of thirty-nine patients with abnormal electrocardiograms. A negative test was associated with a good recovery and good cardiac function.

The presence of a normal two-step exercise tolerance test, normal ventricular pulsation, or a normal electrocardiogram following coronary occlusion was usually accompanied by complete clinical recovery. Not only were significant angina pectoris and dyspnea uncommon when the foregoing tests became normal but a subsequent attack of either coronary occlusion or heart failure was rare. In those whose recovery was poor there was nearly always objective evidence of disability.

AUTHORS.

Perera, G. A., and Berliner, R. W.: The Relation of Postural Hemodilution to Paroxysmal Dyspnea. *J. Clin. Investigation* 22: 25, 1943.

It has been confirmed that serum protein concentrations are considerably altered in health and disease by changes in position and by muscular activity.

This decrease in serum protein concentration appears to be the result of hemodilution, due to an increase in plasma volume.

The close correlation between nocturnal hemodilution and attacks of paroxysmal dyspnea suggests that an increase in plasma volume is an important factor in the production of acute left-sided failure in individuals with organic heart disease.

Clinical interpretations of protein values must be made with caution since an average fall of 0.8 Gm. per 100 c.c. is encountered after rest in the horizontal position.

AUTHORS.

Yeomans, A., Porter, R. R., and Swank, R. L.: Observations on Certain Manifestations of Circulatory Congestion Produced in Dogs by Rapid Infusion. *J. Clin. Investigation* 22: 33, 1943.

Rapid infusion in dogs produced congestion in the peripheral, pulmonary and portal venous systems, evidenced by rises in their venous pressures; swelling of the abdomen, liver, and spleen, and in some cases, pulmonary edema; an increase in plasma volume and a dilution of the serum proteins; an increase in the heart rate, heart size, and cardiac output; gallop rhythm and systolic murmur; and an increase in oxygen consumption.

These phenomena and their relationship to congestive failure in humans are discussed. An explanation is offered for the stabilization of the peripheral venous pressure, which takes place during infusion.

AUTHORS.

Warren, S.: *Effects of Radiation on Normal Tissues. VI. Effects of Radiation on the Cardiovascular System.* Arch. Path. 34: 1070, 1942.

An extensive review of the literature on the effects of roentgen radiation. This is a section of a more general review on other parts of the body. Includes as well the effect of radium and other active agents.

McCulloch.

Sigler, L. H.: *Trauma of the Heart Due to Nonpenetrating Chest Injuries.* J. A. M. A. 119: 855, 1942.

Trauma of the heart and the adjoining structures caused by blows to the chest or to distant parts of the body occurs much more often than the literature would indicate. This paper describes briefly the results of the available experimental work on the subject, the types of force that may produce cardiac injury in man and the resulting form of injury. The symptom complex and electrocardiographic manifestations of cardiac injury are briefly described. Emphasis is placed on the importance of bearing in mind the possibility that trauma of the heart may occur in any bodily injury, and of subjecting such patients to frequent cardiac examinations, including repeated electrocardiographic studies.

AUTHOR.

Wakerlin, G. E., Johnson, C. A., Smith, E. L., Moss, W. G., and Weir, J. R.: *Prophylactic Treatment of Experimental Renal Hypertension With Renin.* Am. J. Physiol. 137: 515, 1942.

Studies were made of the prophylactic effects of partially purified hog renin, inactivated hog renin, dog renin, rabbit renin, inactive human renin, and liver extract prepared like renin, in experimental renal hypertension in the dog.

Hog renin completely protected two dogs, partially protected one, and did not protect a fourth animal against the development of experimental renal hypertension following constriction of the renal arteries by the Goldblatt technique.

Inactivated hog renin protected one dog but did not protect three other animals.

Dog renin completely protected one dog, partially protected one, and did not protect two dogs.

Rabbit renin completely protected one dog against experimental renal hypertension.

Inactive human renin offered no protection to two dogs and liver extract was likewise ineffective in three dogs.

Sixteen untreated control animals all developed experimental renal hypertension following constriction of the renal arteries.

The mechanism of these prophylactic effects is not apparent at present. They may be due to renin or to some other substance in the partially purified renal extracts. Antirenin is almost certainly not involved. Further studies which may clarify the mechanism are now under way.

AUTHORS.

Burlingame, P., Long, J. A., and Ogden, E.: *The Blood Pressure of the Fetal Rat and Its Response to Renin and Angiotonin.* Am. J. Physiol. 137: 473, 1942.

Injection of an effective dose of renin into the blood stream of rats in late pregnancy does not affect the fetal blood pressure. Injection of even larger doses of renin, angiotonin and adrenalin into the maternal blood stream cause a profound fall in fetal blood pressure. Recovery is slow and incomplete.

Injections of renin, angiotonin and adrenalin into the fetal blood stream cause a pronounced rise in fetal blood pressure.

With renin, tachyphylaxis was demonstrated in both mother and fetus independently but was not transferred from one to the other.

Injections of renin and angiotonin large enough to raise the maternal blood pressure when injected directly into the maternal circulation, fail to do so if injected into the fetal circulation.

The fetus is very much less responsive to renin, angiotonin and epinephrine than the mother.

AUTHORS.

Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3-3'-Methylenebis (4-Hydroxycoumarin) (Dicoumarin). *Am. J. M. Sc.* 205: 24, 1943.

The effect of the synthetic compound 3-3'-methylenebis (4-hydroxycoumarin) —dicoumarin—upon the coagulation of blood and upon certain blood constituents was studied in detail in a small group of patients.

The drug was found to act by diminishing the effective prothrombin concentration in the blood, sometimes to very small amounts.

The prolonged blood coagulation time observed is apparently secondary to the low prothrombin concentration, but was not constant nor was it of marked degree unless large doses of the drug are administered.

The coagulation time measured in "Lusteroid," although more variable than in glass, showed much greater delay in clotting than in glass after the administration of the drug. The suggestion was made that the coagulation time in "Lusteroid" indicates the true coagulation defect more closely than does glass.

The occurrence of prothrombin clotting times longer than recalcified plasma clotting time was observed and the possible significance of the finding discussed.

The relation of the abnormal clotting mechanism to other coagulation factors: foreign surface, platelets, "globulin substance," and plasma proteolytic enzyme was studied and the results discussed.

The effect of the administration of the drug upon blood cytology, liver function, plasma proteins, especially fibrinogen, was studied and no significant abnormalities found.

Vitamin K (synthetic) was found not to act in any way as an antidote to the effect of administration of the drug.

Whole blood transfusion was found to have only a transitory effect or no effect upon the abnormal clotting mechanism in patients receiving the drug.

It is suggested that the variable effect of the drug upon blood coagulability, its prolonged action after discontinuation, and its difficulty in control render the drug a poor heparin substitute, and that great caution must be used in its administration.

AUTHORS.

Taylor, R. D., and Page, I. H.: The Effect of Antipressor Kidney Extract, Angiotonin, Methyl Guanidine and Tyramine on Cardiac Output as Measured by the Ballistocardiograph in Hypertensive and Normal Persons. *Am. J. M. Sc.* 205: 66, 1943.

The cardiac effects of tyramine, and less so of methyl guanidine, as measured by the ballistocardiograph are such as to make it unlikely that they participate in the genesis of renal hypertension. On the contrary, angiotonin exhibits properties which are consonant with those anticipated from knowledge of the cardiodynamics in hypertension. This view is strengthened by the observation that antipressor,

angiotonin-destroying extracts of kidneys, administered to hypertensive patients, abolish at least one characteristic action of angiotonin, i.e., they increase the depressed cardiac output.

AUTHORS.

Zurrow, H., Saland, G., Klein, C., and Goldman, S.: The Effect of Testosterone Propionate in the Treatment of Arteriosclerosis Obliterans. *J. Lab. & Clin. Med.* 28: 269, 1942.

Twenty-three patients suffering from obliterative vascular disease of the lower extremities were studied to note the effect of testosterone propionate on the signs and symptoms of their disease. Eight cases received biweekly intramuscular injections of 25 mg. of testosterone propionate; fifteen patients were observed as controls. The entire study was carried on over a period of eighteen months.

No significant effect was noted in the treated cases with respect to vascular anatomic status, tissue anatomic status, vascular reserve, claudication, rest. pain, or functional status, as compared with the control cases.

AUTHORS.

Goodman, J. I., Corsaro, J. F., and Stacy, R.: Mercurial and Xanthine Diuretics in Chronic Congestive Heart Failure: A Comparative Survey. *Arch. Int. Med.* 70: 975, 1942.

It is proposed that accurate clinical methods for the evaluation of mercurial and xanthine diuretics in patients with hydropic cardiac disease require a preliminary period of treatment until all grossly visible edema has disappeared. This disappearance has been determined from the strict use of the daily weight of the patient, and the resultant condition has been called by us a "state of balance."

In patients in this "state of balance" only the really effective diuretics are capable of producing a further diuresis.

The following observations were made on sixteen patients given a total of 278 injections:

Injectable preparations in which mersalyl solution was combined with theophylline or theophylline with ethylenediamine were notably less efficient than pure mersalyl solution administered in similar doses.

Oral and rectal modes of therapy which employed combinations of mersalyl solution and theophylline produced little diuretic effect compared with that produced by injectable preparations administered to the same patients.

Theophylline with ethylenediamine ($7\frac{1}{2}$ grains) given intravenously to patients in a "state of balance" did not produce any evident diuresis by itself.

Finally, the greatest diuresis was produced by mersalyl solution (1 c.c.) given intramuscularly one hour after intravenous administration of theophylline with ethylenediamine ($7\frac{1}{2}$ grains). A superior degree of diuresis resulted, which was equalled only by a dose of mersalyl solution alone containing four times as much mercury, namely, 4 c.c.

AUTHORS.

Campbell, M.: Partial Heart Block Due to Digitalis. *Brit. Heart J.* 4: 131, 1942.

Digitalis therapy is one of the commonest causes of partial heart block with dropped beats, and a common cause of a P-R interval that is much prolonged without dropped beats. Other factors, however, are generally present, and the most important of these seems to be some lengthening of the P-R interval before digitalis therapy; even then, a concurrent infection is often the immediate cause of the dropped beats.

In a series of cases of partial heart block nearly 40 per cent of those with dropped beats were being given digitalis, and 15 per cent of those with latent heart block.

The most essential prerequisite was some prolongation of the P-R interval before treatment. In those with partial heart block and dropped beats, and in those with latent heart block, it averaged 0.21 second. Only in three of twenty-three was the P-R interval below 0.18 second; in these three it was 0.16 second, and in two of them there was acute infection also. When there were no dropped beats, the P-R interval was on the average increased to 0.26 second. When there were dropped beats, there were most often two responses before the dropped beat, and the lengthening P-R intervals averaged 0.22 second, 0.37 second, dropped beat, etc. This, however, was the average of very varied figures, which averaged 0.22, 0.29, dropped beat, etc.; in three, and 0.22, 0.41, dropped beat, etc., in six patients. No special difference could be found between the groups with these different responses. Apart from the presence of latent heart block the etiology of the underlying heart disease did not seem of importance, though, naturally, congestive failure was present in the majority, as this was usually the indication for digitalis.

The presence of a concurrent infection seemed the next most important factor. When there were dropped beats, more than half had some active infection at the time. Sometimes this was a severe infection such as active rheumatic carditis, but often it seemed of a trivial nature, and it was only because digitalis could be taken at other times without producing dropped beats, or because the rise of temperature ran so closely parallel to their onset, that one could be sure of the connection. When there was latent heart block, an active infection was less often present, but was noted as the cause in a few cases. In others where there was no infection but a heart that was very seriously damaged (as shown by the patient's death within a relatively short time), this seemed an additional factor, making the conduction time more sensitive to digitalis than usual.

Large amounts of digitalis were rarely the cause. Three of these cases were taking amounts that would generally be thought excessive (and curiously enough two of these had acute infections at the time, and there seemed no reason why any digitalis should have been given); seven had amounts that were large, but quite reasonable; and twenty-two were taking amounts that were average or sometimes even small.

In general, there seemed to be no severe ill effects, even when there were dropped beats; and the block passed off quickly (within two or three days), but, of course, this immunity is dependent on the heart block being recognized quickly.

There seems no reason why the chance finding of latent heart block should prevent adequate treatment with digitalis where this is indicated, though naturally the case should be watched even more carefully than usual.

AUTHORS.

Shleser, I. H., and Asher, R.: Efficacy of Adrenal Cortical Extract and of Paredrine in the Prevention of Experimental Shock Following Venous Occlusion of a Limb. *Am. J. Physiol.* 138: 1, 1942.

Adrenal cortical extract (ACE) is a beneficial therapeutic agent in the treatment of shock following venous occlusion of a limb.

ACE shows a definite tendency to reduce the amount of fluid lost into the edematous limb, an action more striking than that of desoxycorticosterone acetate (DCA) alone. However, it has a less marked effect on survival than DCA.

Paredrine, a vasopressor substance, is of no benefit in shock in which the initiating factor is an escape of plasma fluid, since it appears to augment the escape of fluid through capillaries with impaired permeability.

AUTHOR.

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*Executive Committee.

Erratum

The two illustrations reprinted here were printed upside down on page 578 of the May issue, in the article by Murnaghan, McGinn, and White, "Pulmonary Embolism With and Without Acute Cor Pulmonale, With Especial Reference to the Electrocardiogram."

Please paste these correctly placed figures over those on page 578.

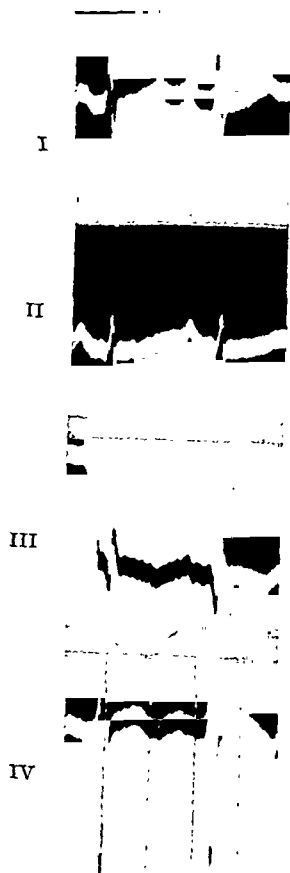


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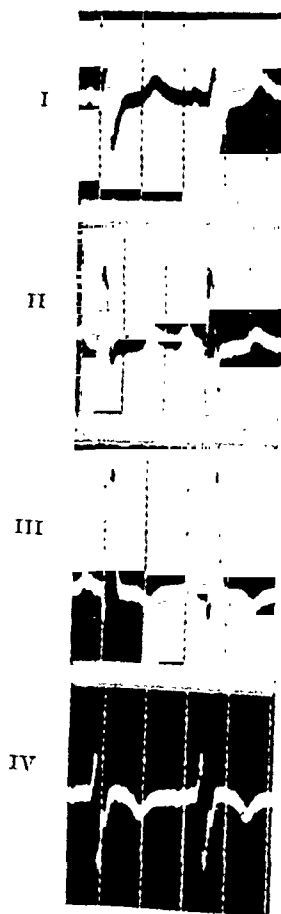


Fig. 3.

Fig. 2.—Case 2, W. R. August 17, 1939, 24 hours after most recent attack.
Fig. 3.—Case 3, F. B. April 24, 1941, 20 hours after first attack, 12 hours after second attack.

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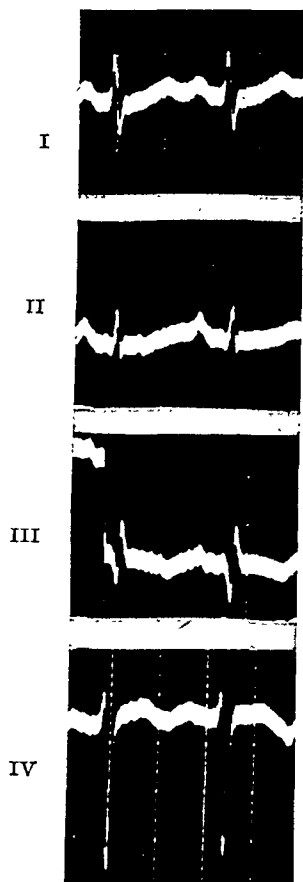


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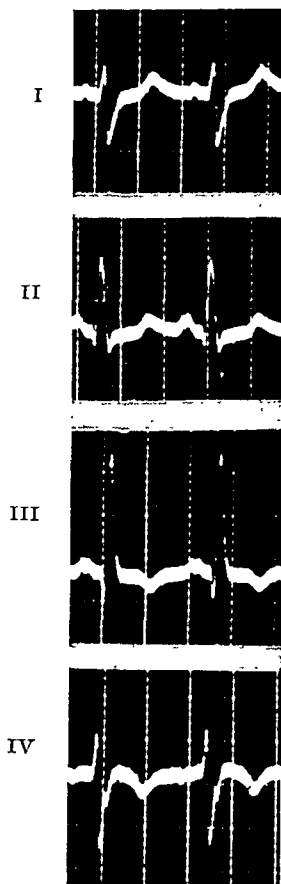


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